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(54) Title: BICYCLIC HYDANTOIN DERIVATIVES AND COMBINATORIAL LIBRARIES THEREOF

(57) Abstract: The present invention relates to novel bicyclic hydantoin derivative compounds of the following formula (I): wherein R^1 to R^5 and n have the meanings provided herein. The invention further relates to combinatorial libraries containing two or more such compounds, as well as methods of preparing bicyclic hydantoin derivative compounds.

BICYCLIC HYDANTOIN DERIVATIVES AND COMBINATORIAL LIBRARIES THEREOF

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to the synthesis of compounds comprising heterocyclic rings. In one embodiment, the invention provides novel bicyclic hydantoin derivative compounds as well as novel combinatorial libraries comprised of such compounds.

BACKGROUND INFORMATION

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested, one or more structures is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional "one-at-a-time" synthesis and biological testing of analogs, this optimization process is long and labor intensive. Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional "one-at-a-time" synthesis methods, except over a time frame of years or even decades. Faster methods are needed that allow for the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it comes to synthesizing more complex compounds, such as bicyclic hydantoin derivative compounds.

Combinatorial approaches have been extended to "organic," or non-peptide, libraries. Combinatorial chemical methods have even been extended to hydantoin derivative compounds, as described, for example, in DeWitt et al., *Proc. Natl. Acad. Sci. USA*, 90:6909-6913 (1993); Dressman et al., *Tetr. Lett.*, 37:937-940 (1996); Hanessian et al., *Tetr. Lett.*, 33:5835-5838 (1996); Kim et al., *Tetr. Lett.*, 38:4603-4606 (1997); Yoon et al., *Chem. Commun.*, 2703-2704 (1998); Wilson et al., *Tetr. Lett.*, 39:5135-5138 (1998); Chong et al., *Tetr. Lett.*, 40:2493-2496 (1999); Wu et al., *Tetr. Lett.*, 41:1165-1169 (2000); Park et al., *J. Org. Chem.*, 63:113-117 (1998); Gong et al., *Tetr. Lett.*, 39:3379-3382 (1998). Gong et al., *J. Org. Chem.*, 63:3081-3086 (1998); and Gong et al., *J. Org. Chem.*, 63:4854-4856 (1998).

However, the libraries to date contain compounds of limited diversity and complexity. Such compounds are particlularly limited regarding amino and substituted amino radicals attached to the bicyclic hydantoin core.

A need therefore exists to develop more complex libraries based on heterocyclic medicinal compounds which would need less time and effort in the synthesis and testing required to bring an organic pharmaceutical product to fruition. In short, improved methods for generating therapeutically useful heterocyclic compounds, such as bicyclic hydantoin derivatives, are desired.

Hydantoin derivative compounds have been the subject of investigation in a number of different biological areas. For example, hydantoin derivatives have been proposed or used as anticonvulsant, antibacterial, antidiabetic, antiarrhythmic, antifungal

or herbicidal agents. See Spinks et al., *Prog. Med. Chem.*, 3:313 (1963); Wright et al., *J. Med. Chem.*, 12: 379-381 (1969); Carrera et al., *J. Heterocyclic Chem.*, 29:847-852 (1992); Coudert et al., *Pharm. Acta. Helv.*, 66:155-159 (1991); Karolakwojciechowska et al., *Pharmazie*, 50:114 (1995); Issartel et al., *Eur. J. Med. Chem.*, 31:717-723 (1996); Nam et al, *Arch. Pharm.*, 330: 268-270 (1997); U.S. Pat. No. 4,198,423, 1980 (BASF A.-G., Fed. Rep. Ger.); and Mappes et al, *Chem. Abstr.*, 93: 71784 (1980).

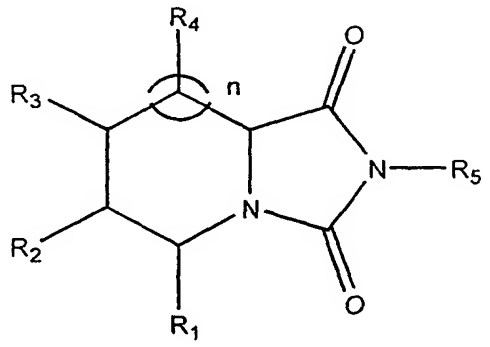
Bicyclic hydantoin derivatives have been the subject of serial chemical synthesis. See, for example, WO 98/2721; Nam et al., *supra.*; WO 96/16111; Issartel et al., *supra.*; WO 93/2413; Evans et al., *J. Med. Chem.*, 36: 3993-4005 (1993); EP 91-810980; and JP 78-114787. However, more complex bicyclic hydantoin derivatives, especially those with a nitrogen substitution (i.e., amino, (mononsubstituted)amino or (disubstituted)amino) on the non-hydantoin ring, have been difficult to attain even through serial methods.

This invention satisfies this need and provides related advantages as well. The present invention overcomes the known limitations to classical serial organic synthesis of bicyclic hydantoin derivatives, for example, as well as the shortcomings of combinatorial chemistry related to bicyclic hydantoin derivatives. The present invention allows for rapid generation of large diverse libraries of complex bicyclic hydantoin derivatives as discrete molecules. The present invention can utilize a readily available pool of building blocks that can be incorporated into the various regions of the molecule. Furthermore, the method of making the present invention allows for the use of building blocks that

contain a wide range of diverse functionality. Such building blocks can provide combinatorial libraries that consist of large numbers as well as combinatorial libraries that are extremely diverse with respect to the functionality contained within those libraries. The present invention combines the techniques of solid-phase synthesis of bicyclic hydantoin derivatives and the general techniques of synthesis of combinatorial libraries to prepare highly diverse new bicyclic hydantoin derivative compounds.

SUMMARY OF THE INVENTION

The present invention relates to novel bicyclic hydantoin derivative compounds of the following formula:



wherein R^1 to R^5 and n have the meanings provided herein.

The invention further relates to combinatorial libraries containing two or more such compounds, as well as methods of preparing bicyclic hydantoin derivative compounds.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows Scheme 1 for the combinatorial synthesis of bicyclic hydantoin derivative compounds, where n is 0 and the depicted exocyclic nitrogen is attached to a sulfonyl derivative ($-S(O_2)R_2$). The reagents and conditions for each step of Scheme 1 are as follows: step (a): t-Boc-NH-R_1-CO_2H, DIEA (N,N-diisopropylethylamine), DIC (diisopropylcarbodiimide), HOBt (1-hydroxybenzotriazole) and DMF (N,N-dimethylforamide) for 20 hours; step (b) 55% TFA (trifluoroacetic acid) and DCM (dichloromethane) for 30 minutes; step (c) R_2SO_2Cl, DIEA and DCM for 48 hours; step (d) trans-L-t-Boc-4-Hyp-OMe, (hyp = hydroxyproline), Ph_3P (triphenylphosphine), DIAD, (diisopropyl azodicarboxylate), NMM (N-methylmorpholine), DCM and THF (tetrahydrofuran) for three days; step (e) 55% TFA/DCM for 30 minutes; step (f) R_3NCO and DMF for 3 days; step (g) 0.025 M TMG/DMF (tetramethylguanidine) for 16 hours; and step (h) gaseous HF (hydrofluoride) for 2 hours.

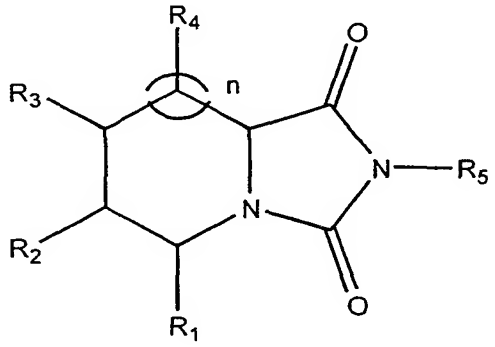
Figure 2 shows Scheme 2 for the combinatorial synthesis of bicyclic hydantoin derivative compounds, where n is 0 or 1, R_2 or R_3 is -OH (as shown between steps c and d) and the depicted exocyclic nitrogen is attached to a sulfonyl derivative ($-S(O_2)R_{11}$; as shown between steps d and e and thereafter). The reagents and conditions for each step of Scheme 2 are as follows: step (a): t-Boc-NH-R_1-CO_2H, DIEA, DIC, HOBt and DMF for 20 hours; step (b) 55% TFA/DCM for 30 minutes; step (c) R_2SO_2Cl, DIEA and DCM for 48 hours; step (d) for three days, Ph_3P, DIAD, NMM, DCM, THF and (i) for n=0, a 4-hydroxy-N-Boc-proline ester derivative; (ii) for n=1, a 4- or 5-hydroxy-N-Boc-pipecolinate derivative; step (e)

55% TFA/DCM for 30 minutes; step (f) R_3NCO and DMF for 3 days; step (g) 0.025 M TMG/DMF for 16 hours; and step (h) gaseous HF (hydrofluoride) for 2 hours.

Figure 3 shows Scheme 3 for the combinatorial synthesis of bicyclic hydantoin derivative compounds, wherein n is 0, 1 or 2 and using an alternate scheme, resin and resin attachment position. The reagents and conditions for each step of Scheme 3 are as follows: step (a): DIEA, DIC (N,N'-diisopropylcarbodiimide) HOBt and DMF for 20 hours; step (b) 20% piperidine in DMF or 55% TFA/DCM for 30 minutes; step (c) R_5NCO, DIEA and DMF for 20 hours; step (d) catalytic TMG/DMF or catalytic barium dihydroxide in DMF.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds and combinatorial libraries of compounds of the formula:



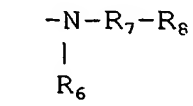
wherein:

n is 0, 1 or 2;

a) R_1; b) when n is 0, R_3; c) when n is 1, R_4 and one of R_2 and R_3; and d) when n is 2 an addition radical between R_3 and R_4, R_{34}, is present and, when n is 2, R_4 and two of R_2,

R_3 and R_{34}:
are each independently a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, carboxy or protected carboxy; and

a) when n is 0, R_2; b) when n is 1, one of R_2 and R_3; and c) when n is 2 one of R_2, R_3 and R_{34}:
is amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino or the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is -C(O)-, -C(O)O- or $-S(O)_2-$ and M is a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle or substituted heterocycle;

R_7 is the formula -D-W-E-, wherein at least one of D, W and E is present and the other two are optionally present or absent, and wherein:

W is C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene or substituted heteroarylene; and D, which, if present, is directly attached to the nitrogen depicted in the formula, and E are independently C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene or C_2 to C_{12} substituted alkynylene;

R_8 is a hydrogen atom, a halide, $-OR_9$, $-CO_2R_9$, $-C(O)NR_9R_{10}$ or $-NR_9R_{10}$, wherein R_9 and R_{10} are independently a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl or substituted phenylaminothiocarbonyl; and

R_5 is a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted

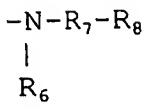
alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, heterocyclic ring or substituted heterocyclic ring, or (i) the formula $-C(O)R_{11}$; (ii) the formula $-C(O)OR_{11}$; (iii) the formula $-C(O)NHR_{11}$; (iv) the formula $-C(O)NR_{11}R_{12}$; or (v) the formula $-S(O_2)R_{11}$, wherein R_{11} and R_{12} are, independently, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, heterocyclic ring or substituted heterocyclic ring, or R_5, together with the adjoining nitrogen atom depicted in the formula, form a heterocyclic ring or substituted heterocyclic ring, wherein said ring is non-aromatic.

In a further embodiment of the present invention, n is 0.

In an additional embodiment, R_1 and R_3 are each a hydrogen atom.

In another embodiment,

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl or substituted heteroaryl;

R_7 is the formula -D-W-, wherein D is present and W is optionally present or absent, and wherein:
D is C_1 to C_{12} alkylene or C_1 to C_{12} substituted alkylene; and W is C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, arylene or substituted arylene; and

R_8 is $-C(O)NR_9R_{10}$, wherein one of R_9 and R_{10} is a functionalized resin and a hydrogen atom, and the other is a hydrogen atom.

In an additional embodiment,

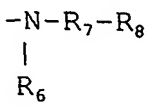
R_5 is C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl or C_7 to C_{18} substituted phenylalkyl.

A further embodiment of the present invention provides a combinatorial library or single compound wherein:

n is 0;

R_1 and R_3 are each a hydrogen atom;

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is thiophen-2-yl, phenyl, 2,5-dichlorophenyl, 2-nitrophenyl, 4-bromophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-(trifluoromethyl)phenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 2,3-dichlorophenyl, 2-bromophenyl, 5-(2-pyridyl)thiophen-2-yl, 2-chloro-5-(trifluoromethyl)phenyl, 4-cyanophenyl, 2-cyanophenyl, 5-chloro-1,3-dimethylpyrazol-4-yl, 3,5-dimethylisoxazol-4-yl, 2,4-dichlorophenyl, 2-chloro-4-(trifluoromethy)lphenyl, 2-chloro-4-fluorophenyl, 2,4,6-trichlorophenyl, 1-methylimidazol-4-yl, 2-methoxycarbonythiophen-3-yl, 5-(isoxazol-3-yl)thiophen-2-yl, 4-phenylphenyl, 3,4-difluorophenyl, 3-methyl-5-chlorobenzothiophen-2-yl, 3-cyanophenyl, 4-methylsulfonylphenyl or 2-methylsulfonylphenyl;

R_7 is the formula -D-W-, wherein:
W is absent and D is phenylethyl-1-ene, ethyl-1-ene, propyl-1-ene, propylene, pentylene, 4-(chlorophenyl)ethyl-1-ene, 3-(methylthio)propyl-1-ene, 4-(methoxyphenyl)ethyl-1-ene, 2-methylpropyl-1-ene, 2-

(4-imidazole)ethyl-1-ene; 2-(benzyloxy)ethyl-1-ene, 3-methylbutyl-1-ene or 2-cyclohexylethyl-1-ene; or D is methylene and W is 4-phenylene or 4-cyclohexylene; and

R_8 is $-C(O)NH_2$; and

R_5 is phenyl, 2-bromophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2-methoxyphenyl, O-tolyl, 2-ethylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, m-tolyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, p-tolyl, 1-naphthyl, benzyl, 2-isopropylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2-ethyl-6-methylphenyl, 3-(methylthio)phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2-methoxy-5-methylphenyl, 3-ethylphenyl, 4-ethoxyphenyl, 4-(methylthio)phenyl, 4-isopropylphenyl, 4-ethylphenyl, 4-n-butylphenyl, 2-isopropyl-6-methylphenyl, 2,4,5-trimethylphenyl, 4-butoxyphenyl, 5-fluoro-2-methylphenyl or 4-(dimethylamino)phenyl.

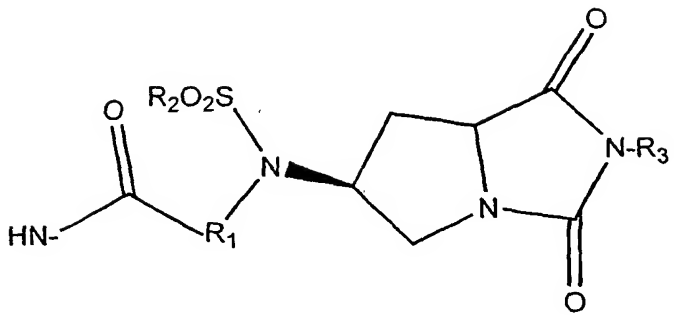
The invention also provides methods of preparing bicyclic hydantoin derivative compounds and combinatorial libraries. In one method, as shown in Figure 1, such compounds can be prepared by (1) coupling (a) a molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$, wherein R_1 and R_2, independently, are each a variable group, with (b) a ring nitrogen compound that is substituted at the position adjacent to the ring nitrogen (the 2 position) with -C(O)-O-alkyl, where the alkyl group is preferably ethyl or methyl, and where the ring is further substituted with a hydroxy group, resulting a ring nitrogen compound that is substituted at the position adjacent to the ring nitrogen with -C(O)-O-alkyl and further substituted with a group of the

formula $-N(S(O_2)-R_2)-R_1-C(O)-NH-$ (see step d of Figure 1 and step d of Figure 2); (2) reacting the resulting compound of step (1) with an isocyanate of the formula R_3-NCO, where R_3 is a variable group, to form a $-C(O)-NH-R_3$ group attached to the ring nitrogen (1 position); and (3) cyclizing the resulting compound of step (2) by reacting it with a base to form a bicyclic hydantoin derivative. Exemplary bases include tetramethylguanidine and barium hydroxide.

The method further provides where the molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ is attached to a functionalized resin. The method also provides that the molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ is formed by coupling a molecule containing a group of the formula $-NH-C(O)-R_1-NH_2$ with $R_2-S(O_2)-$leaving group, preferably, where the leaving group is a halide and, more preferably, where the halide is chloride.

The method additionally provides where the ring nitrogen compound is a pyrrolidine derivative and,

therefore, the resulting compound of step (3) is of the formula:



The method also provides where the ring nitrogen compound is a piperidine derivative (e.g, a six-member ring) and where it is a seven-member ring. It should be understood that the ring nitrogen can be fused with another ring, for example, an aromatic ring. It should also be understood that, where, the ring is six or seven member, it can contain a double bond. However, the ring should not be aromatic.

Another method of the present invention provides (1) coupling (i) a ring nitrogen compound, wherein said ring is non-aromatic, wherein said ring is attached to a group containing -C(O)-O-, said ring directly attached from a position adjacent to the ring nitrogen to the carbonyl carbon of said -C(O)-O-, with (ii) an isocyanate derivative of the formula variable-NCO to form (iii) a ring nitrogen compound with the group -C(O)-NH-variable directly attached to the ring nitrogen; and (b) cyclizing the resulting compound of step (1) by reacting it with a base to form a bicyclic hydantoin derivative. Exemplary bases include tetramethylguanidine and barium hydroxide.

The method further provides where the group

containing -C(O)-O- is attached to a functionalized resin (via oxygen). The method also provides where the ring nitrogen is five- six- or seven-member (see Figure 3). It should be understood that the ring nitrogen can be fused with another ring, for example, an aromatic ring. It should also be understood that, where, the ring is six or seven member, it can contain a double bond. However, the ring should not be aromatic.

When the above-described compounds include one or more chiral centers, the stereochemistry of such chiral centers can independently be in the R or S configuration, or a mixture of the two. The chiral centers can be further designated as R or S or R,S or d,D, l,L or d,l, D,L.

Regarding the compounds and combinatorial libraries described herein, the suffix "ene" added to any of the described radical terms means that the radical is connected to two parts of the compound (for example, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), etc.).

The term "C_1 to C_{12} alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. Preferred "C_1 to C_{12} alkyl" groups are methyl, ethyl, iso-butyl, sec-butyl and iso-propyl. Similarly, the term "C_1 to C_{12} alkylene" denotes radicals of 1 to 12 carbons connected to two other parts in the compound.

The term "C_2 to C_{12} alkenyl" denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl,

5-heptenyl, 6-heptenyl, (as well as octenyl, nonenyl, decenyl, undecenyl, dodecenyl radicals attached at any appropriate carbon position and the like) as well as dienes and trienes of straight and branched chains.

The term "C_2 to C_{12} alkynyl" denotes such radicals as ethanol, propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 2- hexynyl, 3-hexynyl, 4-hexynyl, 2-heptynyl, 3-heptynyl, 4- heptynyl, 5-heptynyl (as well as octynyl, nonynyl, decynyl, undecynyl, dodecynyl radicals attached at any appropriate carbon position and the like) as well as di- and tri-ynes of straight and branched chains.

The terms "C_1 to C_{12} substituted alkyl," "C_2 to C_{12} substituted alkenyl," "C_2 to C_{12} substituted alkynyl," "C_1 to C_{12} substituted alkylene," "C_2 to C_{12} substituted alkenylene" and "C_2 to C_{12} substituted alkynylene" denote groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, C_3 to C_7 cycloalkyl, phenyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1 to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{10} alkylthio or C_1 to C_{10} alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1- iodoethyl, 2-iodoethyl, 1-chloropropyl, 2-chloropropyl, 3- chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1- iodopropyl, 2-iodopropyl, 3-iodopropyl, 2-aminoethyl, 1- aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

Examples of the above substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted alkenyl can be used.

Examples of the above substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen atom doubly bonded to the carbon atom, thereby forming a ketone moiety.

The term "protected oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with two alkoxy groups or twice bonded to a substituted diol moiety, thereby forming an acyclic or cyclic ketal moiety.

The term "C_1 to C_{12} alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is methoxy. The term "C_1 to C_{12} substituted alkoxy" means the alkyl portion of the alkoxy can be substituted in the same manner as in relation to C_1 to C_{12} substituted alkyl. Similarly, the term "C_1 to C_{12} phenylalkoxy" as used herein means "C_1 to C_{12} alkoxy" bonded to a phenyl radical.

The term "C_1 to C_{12} acyloxy" denotes herein groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, undecanoyloxy, dodecanoyloxy and the like.

Similarly, the term "C_1 to C_{12} acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, benzoyl and the like. Preferred acyl groups are acetyl and benzoyl.

The term "C_1 to C_{12} substituted acyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring,

imidazolyl, indolyl, pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, C_1 to C_{12} alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1 to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{12} alkylthio or C_1 to C_{10} alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of C_1 to C_{12} substituted acyl groups include 4-phenylbutyroyl, 3-phenylbutyroyl, 3-phenylpropanoyl, 2- cyclohexanylacetyl, cyclohexanecarbonyl, 2-furanoyl and 3-dimethylaminobenzoyl.

The substituent term "C_3 to C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. Similarly, a substituent that can be C_3 to C_7 cycloalkyl" can also be "C_5 to C_7 cycloalkyl," which includes the cyclopentyl, cyclohexyl or cycloheptyl rings.

The substituent term "C_3 to C_7 substituted cycloalkyl" or "C_5 to C_7 substituted cycloalkyl" indicates the above cycloalkyl rings substituted by one or two halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio,

phenylsulfoxide, phenylsulfonyl, amino, or protected amino groups.

The term "cycloalkylene" means a cycloalkyl, as defined above, where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted cycloalkylene" means a cycloalkylene where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups and further bearing at least one additional substituent.

The term "C_5 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted C_5 to C_7 cycloalkenyl" denotes the above C_5 to C_7 cycloalkenyl rings substituted by a C_1 to C_{12} alkyl radical, halogen, hydroxy, protected hydroxy, C_1 to C_{12} alkoxy, trifluoromethyl, carboxy, protected carboxy, oxo, protected oxo, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

The term "C_5 to C_7 cycloalkenylene" is a cycloalkenyl ring, as defined above, where the cycloalkenyl radical is bonded at two positions connecting together two separate additional groups. Examples of C_5 to C_7 cycloalkenylenes include 1,3-cyclopentylene and 1,2-cyclohexylene.

Similarly, the term "substituted C_5 to C_7 cycloalkenylene" means a cycloalkenylene further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10}

substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group. Examples of substituted C_5 to C_7 cycloalkenylenes include 4-chloro-1,3-cyclopentylene and 4-methyl-1,2-cyclohexylene.

The term "heterocycle" or "heterocyclic ring" denotes optionally substituted five-membered to eight-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered to eight-membered rings may be saturated, fully unsaturated or partially unsaturated, with fully saturated rings being preferred. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, 2-amino-imidazoyl, tetrahydrofurano, pyrrolo, tetrahydrothiophen-yl, hexylmethyleneimino and heptylmethyleneimino.

The term "substituted heterocycle" or "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino,

(disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, heterocycle or substituted heterocycle groups.

The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, oxazolo, isoxazolo, phthalimido, thiazolo and the like.

The term "substituted heteroaryl" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

The term "C_7 to C_{18} phenylalkyl" denotes a C_1 to C_{12} alkyl group substituted at any position within the alkyl chain by a phenyl. The definition includes groups of the formula: -phenyl-alkyl, -alkyl-phenyl and -alkyl-phenyl-alkyl. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{18} phenylalkyl groups are any one of the preferred alkyl groups described herein combined with a phenyl group.

Similarly, the term "C_1 to C_{12} heterocycloalkyl" denotes a C_1 to C_{12} alkyl group substituted at any position within the alkyl chain by a "heterocycle," as defined herein. The definition includes groups of the formula: -heterocyclic-alkyl, -alkyl-heterocyclic and -alkyl-heterocyclic-alkyl. Examples of such a group include 2-pyridylethyl, 3-pierydyl(n-propyl), 4-furylhexyl, 3-piperazyl(n-amyl), 3-morpholyl(sec-butyl) and the like. Preferred C_1 to C_{12} heterocycloalkyl groups are any one of the preferred alkyl groups described herein combined with any one of the preferred heterocycle groups described herein.

The terms "C_7 to C_{18} substituted phenylalkyl" and "C_1 to C_{12} substituted heterocycloalkyl" denote a C_7 to C_{18} phenylalkyl group or C_1 to C_{12} heterocycloalkyl substituted (on the alkyl or, where applicable, phenyl or heterocyclic portion) with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} alkyl, C_1 to C_{12} substituted

alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-(C_1 to C_{12} dialkyl)carboxamide, cyano, N-(C_1 to C_{12} alkylsulfonyl)amino, thiol, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_{12} alkylene or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl, phenyl or heterocyclic groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{18} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-(5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-

aminomethylphenyl)- 3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-*n*-pent-1-yl and the like.

The term "C_7 to C_{18} phenylalkylene" specifies a C_7 to C_{18} phenylalkyl, as defined above, where the phenylalkyl radical is bonded at two different positions connecting together two separate additional groups. The definition includes groups of the formula: -phenyl-alkyl-, -alkyl-phenyl- and -alkyl-phenyl-alkyl-. Substitutions on the phenyl ring can be 1,2, 1,3 or 1,4. C_7 to C_{18} phenylalkylenes include, for example, 1,4-toluylene and 1,3-xylylene.

Similarly, the term "C_1 to C_{12} heterocycloalkylene" specifies a C_1 to C_{12} heterocycloalkyl, as defined above, where the heterocycloalkyl radical is bonded at two different positions connecting together two separate additional groups. The definition includes groups of the formula: -heterocyclic-alkyl-, -alkyl-heterocyclic and -alkyl-heterocyclic-alkyl-.

The terms "C_7 to C_{18} substituted phenylalkylene" and "C_1 to C_{12} substituted heterocycloalkylene" means a C_7 to C_{18} phenylalkylene or C_1 to C_{12} heterocycloalkylene as defined above that is further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio,

phenylsulfoxide, phenylsulfonyl, amino, or protected amino group on the phenyl ring or on the alkyl group.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results.

Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or

4-(n-propyl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

The term "phenoxy" denotes a phenyl bonded to an oxygen atom, wherein the binding to the rest of the molecule is through the oxygen atom. The term "substituted phenoxy" specifies a phenoxy group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino,

(monosubstituted)amino, protected (monosubstituted)amino, protected carboxamide, (disubstituted)amino, carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phenoxy include 2-methylphenoxy, 2-ethylphenoxy, 2-propylphenoxy, 2-isopropylphenoxy, 2-sec-butylphenoxy, 2-allylphenoxy, 2-propenylphenoxy, 2-tert-butylphenoxy, 2-cyclopentylphenoxy, 2-fluorophenoxy, 2-chlorophenoxy, 2-(trifluoromethyl)phenoxy, 2-methoxyphenoxy, 2-ethoxyphenoxy, 2-ethylphenoxy, 2-bromophenoxy, 2-isopropoxyphenoxy, 3-methylphenoxy, 3-tert-butylphenoxy, 3-isopropylphenoxy, 3-pentadecylphenoxy, 3-(trifluoromethyl)phenoxy, 3-fluorophenoxy, 3-chlorophenoxy, 3-bromophenoxy, 3-iodophenoxy, 3-methoxyphenoxy, 3-(trifluoromethoxy)phenoxy, 4-methylphenoxy, 4-ethylphenoxy, 4-propylphenoxy, 4-isopropylphenoxy, 4-sec-butylphenoxy, 4-tert-butylphenoxy, 4-tert-amylphenoxy, 4-nonylphenoxy, 4-dodecylphenoxy, 4-cyclopenylphenoxy, 4-(trifluoromethyl)phenoxy, 4-fluorophenoxy, 4-chlorophenoxy, 4-bromophenoxy, 4-iodophenoxy, 4-methoxyphenoxy, 4-ethoxyphenoxy, 4-(trifluoromethoxy)phenoxy, 4-propoxyphenoxy, 4-butoxyphenoxy, 4-hexyloxyphenoxy, 4-heptyloxyphenoxy, 2,3-dimethylphenoxy, 2,3-dichlorophenoxy, 5,6,7,8-tetrahydro-1-naphthoxy, 2,3-dihydro-2,2-dimethyl-7-benzofuranoxy, 2,3-dimethoxyphenoxy, 2,6-dimethylphenoxy, 2,6-diisopropylphenoxy, 2,6-di-sec-butylphenoxy, 2-tert-butyl-6-methylphenoxy, 2,6-di-tert-butylphenoxy, 2-allyl-6-methylphenoxy, 2,6-difluorophenoxy,

2,3-difluorophenoxy, 2,6-dichlorophenoxy, 2,6-dibromophenoxy, 2-fluoro-6-methoxyphenoxy, 2,6-dimethoxyphenoxy, 3,5-dimethylphenoxy, 5-isopropyl-3-methylphenoxy, 3,5-di-tert-butylphenoxy, 3,5-bis(trifluoromethyl)phenoxy, 3,5-difluorophenoxy, 3,5-dichlorophenoxy, 3,5-dimethoxyphenoxy, 3-chloro-5-methoxyphenoxy, 3,4-dimethylphenoxy, 5-indanoxy, 5,6,7,8-tetrahydro-2-naphthoxy, 4-chloro-3-methylphenoxy, 2,4-dimethylphenoxy, 2,5-dimethylphenoxy, 2-isopropyl-5-methylphenoxy, 4-isopropyl-3-methylphenoxy, 5-isopropyl-2-methylphenoxy, 2-tert-butyl-5-methylphenoxy, 2-tert-butyl-4-methylphenoxy, 2,4-di-tert-butylphenoxy, 2,4-di-tert-amylphenoxy, 4-fluoro-2-methylphenoxy, 4-fluoro-3-methylphenoxy, 2-chloro-4-methylphenoxy, 2-chloro-5-methylphenoxy, 4-chloro-2-methylphenoxy, 4-chloro-3-ethylphenoxy, 2-bromo-4-methylphenoxy, 4-iodo-2-methylphenoxy, 2-chloro-5-(trifluoromethyl)phenoxy, 2,4-difluorophenoxy, 2,5-difluorophenoxy, 3,4-difluorophenoxy, 4-chloro-2-fluorophenoxy, 3-chloro-4-fluorophenoxy, 4-chloro-3-fluorophenoxy, 2-bromo-4-fluorophenoxy, 4-bromo-2-fluorophenoxy, 2-bromo-5-fluorophenoxy, 2,4-dichlorophenoxy, 3,4-dichlorophenoxy, 2,5-dichlorophenoxy, 2-bromo-4-chlorophenoxy, 2-chloro-4-fluorophenoxy, 4-bromo-2-chlorophenoxy, 2,4-dibromophenoxy, 2-methoxy-4-methylphenoxy, 4-allyl-2-methylphenoxy, trans-2-ethoxy-5-(1-propenyl)phenoxy, 2-methoxy-4-propenylphenoxy, 3,4-dimethoxyphenoxy, 3-ethoxy-4-methoxyphenoxy, 4-allyl-2,6-dimethoxyphenoxy, 3,4-methylenedioxyphenoxy, 2,3,6-trimethylphenoxy, 2,4-dichloro-3-methylphenoxy, 2,3,4-trifluorophenoxy, 2,3,6-trifluorophenoxy, 2,3,5-trifluorophenoxy, 2,3,4-trichlorophenoxy, 2,3,6-trichlorophenoxy, 2,3,5-trimethylphenoxy, 3,4,5-trimethylphenoxy, 4-chloro-3,5-dimethylphenoxy, 4-bromo-3,5-dimethylphenoxy,

2,4,6-trimethylphenoxy, 2,6-bis(hydroxymethyl)-4-methylphenoxy, 2,6-di-tert-butyl-4-methylphenoxy, 2,6-di-tert-butyl-4-methoxyphenoxy, 2,4,5- trifluorophenoxy, 2-chloro-3,5-difluorophenoxy, 2,4,6-trichlorophenoxy, 3,4,5-trimethoxyphenoxy, 2,3,5-trichlorophenoxy, 4-bromo-2,6-dimethylphenoxy, 4-bromo-6-chloro-2-methylphenoxy, 2,6-dibromo-4-methylphenoxy, 2,6-dichloro-4-fluorophenoxy, 2,6-dibromo-4-fluorophenoxy, 2,4,6-tribromophenoxy, 2,4,6-triiodophenoxy, 2-chloro-4,5-dimethylphenoxy, 4-chloro-2-isopropyl-5-methylphenoxy, 2-bromo-4,5-difluorophenoxy, 2,4,5-trichlorophenoxy, 2,3,5,6-tetrafluorophenoxy and the like.

The term "C_7 to C_{18} substituted phenylalkoxy" denotes a C_7 to C_{18} phenylalkoxy group bonded to the rest of the molecule through the oxygen atom, wherein the phenylalkyl portion is substituted with one or more, and preferably one or two, groups selected from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-(C_1 to C_{12} dialkyl)carboxamide, cyano, N-(C_1 to C_{12} alkylsulfonyl)amino, thiol, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfonyl groups; and/or the phenyl group can be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl,

hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl) carboxamide, protected N-(C_1 to C_{12} alkyl) carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{16} substituted phenylalkoxy" include groups such as 2-(4-hydroxyphenyl)ethoxy, 4-(4-methoxyphenyl)butoxy, (2R)-3-phenyl-2-amino-propoxy, (2S)-3-phenyl-2-amino-propoxy, 2-indanoxy, 6-phenyl-1-hexanoxy, cinnamyloxy, (+/-)-2-phenyl-1-propoxy, 2,2-dimethyl-3-phenyl-1-propoxy and the like.

The term "phthalimide" means a cyclic imide which is made from phthalic acid, also called 1,2-benzenedicarboxylic acid. The term "substituted phthalimide" specifies a phthalimide group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12}

alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phthalimides include 4,5-dichlorophthalimido, 3-fluorophthalimido, 4-methoxyphthalimido, 3-methylphthalimido, 4-carboxyphthalimido and the like.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

Examples of the term "substituted naphthyl" includes a mono or di(halo)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof and the like; a nitronaphthyl

group such as 3- or 4-nitronaphthyl; a cyanonaphthyl group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2, 4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono- or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3, 4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or 4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-

yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

The term "naphthylene" means a naphthyl radical bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted napthylene" means a naphthylene group that is further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo atoms. There can be one or more halogens, which are the same or different. Preferred halogens are chloro and fluoro.

The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} heterocycloalkyl and C_1 to C_{12} substituted heterocycloalkyl. The (monosubstituted)amino can

additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to an amino group with two substituents chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} acyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocycloalkyl and C_1 to C_{12} substituted heterocycloalkyl,. The two substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen. Similarly, the term "protected N-(C_1 to C_{12} alkyl)carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenylyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl, 1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(p-

toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, -2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyl-oxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxy-carbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenyl-phosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective

Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The term "protected guanidino" as used herein refers to an "amino-protecting group" on one or two of the guanidino nitrogen atoms. Examples of "protected guanidino" groups are described by T.W. Greene and P.G.M. Wuts; M. Bodanzsky; and Stewart and Young, supra.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, (trimethylsilyl)ethyl, (di(n-butyl)methylsilyl)ethyl, p- toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and

can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in *Organic Synthesis*," *2nd ed., John Wiley and Sons*, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxypropyl, 1-ethoxyethyl, methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting groups is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. Related terms are "protected hydroxy," and "protected hydroxymethyl" which refer to a hydroxy or hydroxymethyl substituted with one of the above hydroxy-protecting groups.

The term "C_1 to C_{10} alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups. The term "C_1 to C_{10} alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like. The term "C_1 to C_{10} alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like. it should also be understood that the above thio, sulfoxide or sulfonyl groups can be at any point on the alkyl chain (e.g., 2-methylmercaptoethyl).

The terms "C_1 to C_{10} substituted alkylthio," "C_1 to C_{10} substituted alkylsulfoxide," and "C_1 to C_{10} substituted alkylsulfonyl," denote the C_1 to C_{10} alkyl portion of these groups may be substituted as described above in relation to "substituted alkyl."

The terms "phenylthio," "phenylsulfoxide," and "phenylsulfonyl" specify a thiol, a sulfoxide, or sulfone, respectively, containing a phenyl group. The terms "substituted phenylthio," "substituted phenylsulfoxide," and "substituted phenylsulfonyl" means that the phenyl of these groups can be substituted as described above in relation to "substituted phenyl."

The term "C_1 to C_{12} alkylaminocarbonyl" means a C_1 to C_{12} alkyl attached to a nitrogen of the aminocarbonyl group. Examples of C_1 to C_{12} alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl and butylaminocarbonyl. The term "C_1 to C_{12} substituted alkylaminocarbonyl" denotes a substituted alkyl bonded to

a nitrogen of the aminocarbonyl group, which alkyl may be substituted as described above in relation to C_1 to C_{12} substituted alkyl. Examples of C_1 to C_{12} substituted alkylaminocarbonyl include, for example, methoxymethylaminocarbonyl, 2-chloroethylaminocarbonyl, 2-oxopropylaminocarbonyl and 4-phenylbutylaminocarbonyl.

The term "C_1 to C_{12} alkoxycarbonyl" means a "C_1 to C_{12} alkoxy" group attached to a carbonyl group. The term "C_1 to C_{12} substituted alkoxycarbonyl" denotes a substituted alkoxy bonded to the carbonyl group, which alkoxy may be substituted as described above in relation to "C_1 to C_{12} substituted alkyl."

The term "phenylaminocarbonyl" means a phenyl attached to a nitrogen of the aminocarbonyl group. The term "substituted phenylaminocarbonyl" denotes a substituted phenyl bonded to a nitrogen of the aminocarbonyl group, which phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminocarbonyl include 2-chlorophenylaminocarbonyl, 3-chlorophenylaminocarbonyl , 2-nitorphenylaminocarbonyl, 4-biphenylaminocarbonyl, and 4-methoxyphenylaminocarbonyl.

The term "C_1 to C_{12} alkylaminothiocarbonyl" means a C_1 to C_{12} alkyl attached to an aminothiocarbonyl group, wherein the alkyl has the same meaning as defined above. Examples of C_1 to C_{12} alkylaminothiocarbonyl include methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl and butylaminothiocarbonyl.

The term "C_1 to C_{12} substituted alkylaminothiocarbonyl" denotes a substituted alkyl bonded to an aminothiocarbonyl group, wherein the alkyl

may be substituted as described above in relation to C_1 to C_{12} substituted alkyl. Examples of C_1 to C_{12} substituted alkylaminothiocarbonyl include, for example, methoxymethylaminothiocarbonyl, 2-chloroethylaminothiocarbonyl, 2-oxopropylaminothiocarbonyl and 4-phenylbutylaminothiocarbonyl.

The term "phenylaminothiocarbonyl" means a phenyl attached to an aminothiocarbonyl group, wherein the phenyl has the same meaning as defined above.

The term "substituted phenylaminothiocarbonyl" denotes a substituted phenyl bonded to an aminothiocarbonyl group, wherein phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminothiocarbonyls include 2-chlorophenylaminothiocarbonyl, 3-chlorophenylaminothiocarbonyl, 2-nitorphenylaminothiocarbonyl, 4-biphenylaminothiocarbonyl and 4-methoxyphenylaminothiocarbonyl.

The term "phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of "phenylene" include 1,2-phenylene, 1,3-phenylene, and 1,4-phenylene.

The term "substituted phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups, wherein the phenyl is substituted as described above in relation to "substituted phenyl."

The term "substituted C_1 to C_{12} alkylene" means a C_1 to C_{12} alkyl group where the alkyl radical is connected to two additional groups and further bearing (i.e., substituted with) an additional substituent. Examples of a "substituted C_1 to C_{12} alkylene" include aminomethylene, 1-(amino)-1,2-ethylene, 2-(amino)-1,2-ethylene, 1-(acetamido)-1,2-ethylene, 2-(acetamido)-1,2-ethylene, 2-hydroxy-1,1-ethylene and 1-(amino)-1,3-propylene.

The terms "cyclic C_2 to C_7 alkylene," "substituted cyclic C_2 to C_7 alkylene," "cyclic C_2 to C_7 heteroalkylene," and "substituted cyclic C_2 to C_7 heteroalkylene," defines such a cyclic group bonded ("fused") to the phenyl radical resulting in a bicyclic ring system. The cyclic group may be saturated or contain one or two double bonds. Furthermore, the cyclic group may have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms which are the cyclic C_2 to C_7 heteroalkylene.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different substituents which, if appropriate, can be connected to another part of the compound (e.g., alkylene) selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C_1 to C_4 acyloxy, formyl, C_1 to C_{12} acyl, C_1 to C_{12} alkyl, C_1 to C_7 alkoxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, halo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, hydroxymethyl or a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group fused to the benzene radical can contain two to ten ring members and, preferably, contains three to six members. Examples of such saturated cyclic groups are when the resulting bicyclic ring system is a 2,3-dihydro-indanyl or tetralin ring. When the cyclic groups are unsaturated, the resulting bicyclic ring system can be naphthyl or indolyl. Examples of fused cyclic groups which contain one nitrogen atom and one or more double bonds, preferably one or two double bonds, are when the benzene radical is fused to a pyridino, pyrano, pyrrolo, pyridinyl, dihydropyrrolo, or dihydropyridinyl ring. Examples of fused cyclic groups which contain one oxygen atom and one or two double bonds are when the benzene radical ring is fused to a furo, pyrano, dihydrofurano, or dihydropyrano ring. Examples of fused cyclic groups which have one sulfur atom and contain one or two double bonds are when the benzene radical is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the benzene radical ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl.

One or more of the compounds of the invention, even within a given library, may be present as a salt.

The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, hydrofluoric, trifluoroacetic, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counter-ions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium, sodium, potassium, barium, aluminum and calcium); ammonium and mono-, di- and tri-alkyl amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. See, for example, "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 66:1-19 (1977), which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. For example, a cation for a carboxylate anion will exist when a position is

substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more compounds of the invention, even when in a library, can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups which can be used include the lower alkoxymethyl groups, for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the -(C_1 to C_{12}) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl and the like; the 2-oxo-1,3-diooxlen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl and the like; the C_1 to C_{10} alkylthiomethyl groups, for example methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, -acetoxymethyl and the like; the ethoxycarbonyl-1-methyl group; the -acetoxyethyl; the 1-(C_1 to C_{12} alkyloxycarbonyloxy)ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group; and the 1-(C_1 to C_{12} alkylaminocarbonyloxy)ethyl groups such as the 1-(methylaminocarbonyloxy)ethyl group.

The term "amino acid" includes any one of the twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally-occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), L- or D- naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in the peptide art, such as those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids and amino acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

The term "functionalized resin" means any resin, crosslinked or otherwise, where functional groups have been introduced into the resin, as is common in the art. Such resins include, for example, those functionalized with amino, alkylhalo, formyl or hydroxy groups. Such resins which can serve as solid supports are well known in the art and include, for example, 4-methylbenzhydrylamine-copoly(styrene-1% divinylbenzene) (MBHA), 4-hydroxymethylphenoxymethyl-copoly(styrene-1% divinylbenzene), 4-oxymethyl-phenyl-acetamido-copoly(stryene-1% divinylbenzene)(Wang), 4-(oxymethyl)-phenylacetamido methyl (Pam), and Tentagel™, from Rapp Polymere Gmbh, trialkoxy-diphenyl-methyl ester-copoly(styrene-1% divinylbenzene)(RINK) all of which are commercially available. Other functionalized resins are

known in the art and can be use without departure from the scope of the current invention. Such resins may include those described in Jung, G., Combinatorial Peptide and Nonpeptide Libraries, A Handbook (VCH Verlag, 1996) or Bunin, B. A., The Combinatorial Index (Academic Press, 1998) and are incorporated herein by reference.

As used herein, a "combinatorial library" is an intentionally created collection of differing molecules which can be prepared by the means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). A "combinatorial library," as defined above, involves successive rounds of chemical syntheses based on a common starting structure. The combinatorial libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing their biological activity. The combinatorial libraries will generally have at least one active compound and are generally prepared such that the compounds are in equimolar quantities.

Compounds described in previous work that are not taught as part of a collection of compounds or not taught as intended for use as part of such a collection are not part of a "combinatorial library" of the invention. In addition, compounds that are in an unintentional or undesired mixture are not part of a "combinatorial library" of the invention.

A combinatorial library of the invention can contain two or more of the above-described bicyclic hydantoin compounds. The invention further provides a combinatorial library containing three, four or five or

more of the above-described compounds. In another embodiment of the invention, a combinatorial library can contain ten or more of the above-described compounds. In yet another embodiment of the invention, a combinatorial library can contain fifty or more of the above-described compounds. If desired, a combinatorial library of the invention can contain 100,000 or more, or even 1,000,000 or more, of the above-described compounds.

By way of example, the preparation of the combinatorial libraries can use the "split resin approach." The split resin approach is described by, for example, U.S. Patent 5,010,175 to Rutter, WO PCT 91/19735 to Simon, and Gallop et al., *J. Med. Chem.*, 37:1233-1251 (1994), all of which are incorporated herein by reference.

The amino acids are indicated herein by either their full name or by the commonly known three letter code. Further, in the naming of amino acids, "D-" designates an amino acid having the "D" configuration, as opposed to the naturally occurring L-amino acids. Where no specific configuration is indicated, one skilled in the art would understand the amino acid to be an L-amino acid. The amino acids can, however, also be in racemic mixtures of the D- and L-configuration or the D-amino acid can readily be substituted for that in the L-configuration.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders,

tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the

active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is

divided into unit doses containing appropriate quantities of the active bicyclic hydantoin compound. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

As pharmaceutical compositions for treating infections, pain, or any other indication the compounds of the present invention are generally in a pharmaceutical composition so as to be administered to a subject at dosage levels of from 0.7 to 7000 mg per day, and preferably 1 to 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

The compounds and combinatorial libraries of the invention can be prepared as set forth in Figures 1 to 3 and as described below.

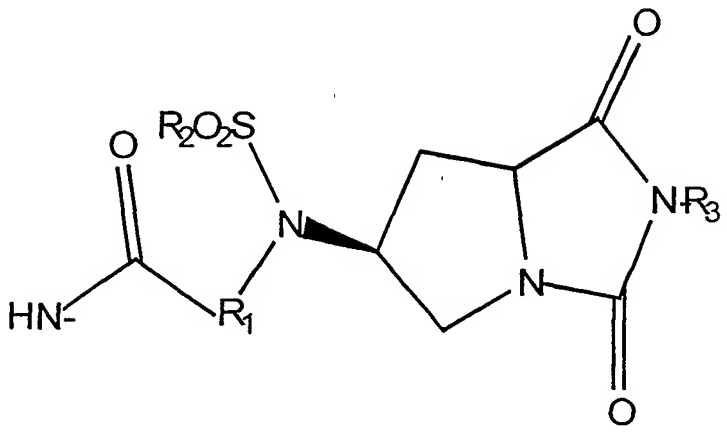
Variant bicyclic hydantoin derivative compounds and combinatorial libraries can be prepared in order to achieve a high level of diversity. For instance, as shown in Figures 1 and 2, such compounds can be prepared by coupling a molecule containing a group of the formula: resin-NH-C(O)-R_1-NH-S(O_2)-R_2, wherein R_1 and R_2, independently, are each a variable group, with (b) a ring

nitrogen compound that is substituted at the position adjacent to the ring nitrogen with $-C(O)-O-CH_3$, resulting a ring nitrogen compound that is substituted at the position adjacent to the ring nitrogen with $-C(O)-O-CH_3$ and further substituted with a group of the formula $-N(S(O_2)-R_2)-R_1-C(O)-NH-$ (see step d of Figure 1 and step d of Figure 2). The resulting compound can then react with an isocyanate of the formula R_3-NCO, where R_3 is a variable group, to form a $-C(O)-NH-R_3$ group attached to the ring nitrogen (see step f of Figure 1 and step f of Figure 2). The resulting compound can then be cyclized in the presence of a base (e.g., tetramethylguanidine) to form a bicyclic hydantoin derivative (see step g of Figure 1 and step g of Figure 2), which can then be cleaved from the resin (see step h of Figure 1 and step h of Figure 2).

The molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ can be attached to a functionalized resin, for example, MBHA, by reacting the amino resin with protected (e.g., t-Boc) amino-R_1-C(O)OH (see step a of Figures 1 and 2) and then deprotecting (see step b of Figures 1 and 2). The molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ can be formed by coupling a molecule containing a group of the formula $-NH-C(O)-R_1-NH_2$ with $R_2-S(O_2)-$leaving group, preferably, where the leaving group is a halide and, more preferably, where the halide is chloride (see step c of Figures 1 and 2).

The the ring nitrogen compound can be five-member (e.g., a pyrrolidine derivative; see step d

of Figure 1) and, therefore, the resulting compound can be of the formula:



(see steps e to h of Figure 1).

However, the ring nitrogen compound can also be a piperidine derivative (e.g, a six-member ring; see steps c and d of Figure 2) and can also be a seven-member ring or even an eight-member ring. It should be understood that, where the ring is greater than five-member, it can contain a double bond. It should also be understood that the ring can be fused to another ring, such as a phenyl ring.

In addition, a ring nitrogen compound with a group containing -C(O)-O- attached (and directly attached to the carbonyl carbon) to a position adjacent to the ring nitrogen (see steps a and b of Figure 3) can be coupled with an isocyanate derivative of the formula variable-NCO to form a ring nitrogen compound with the group -C(O)-NH-variable directly attached to the ring nitrogen (see step c of Figure 3). The resulting compound can be cyclized in the presence of a base, for example, tetramethylguanidine or barium hydroxide, to form a bicyclic hydantoin derivative (see step c of

Figure 3). The group containing -C(O)-O- can be attached to a functionalized resin, for example, via oxygen (see step a of Figure 3). The ring nitrogen can be five- six- or seven or even eight-member (see Figure 3).

Resin-bound bicyclic hydantoin derivative compounds can be cleaved by treating them, for example, with HF. They can also be cleaved with TFA/DCM, provided that TFA sensitive protecting group such as Boc are not used in the synthetic scheme. The compounds can be extracted from the spent resin, for example, with AcOH.

Bicyclic hydantoin derivative compounds and libraries, such as those of the present invention, can be made utilizing individual polyethylene bags, referred to as "tea bags" (see Houghten et al., *Proc. Natl. Acad. Sci. USA* 82: 5131 (1985); *Biochemistry*, 32:11035 (1993); and U.S. Patent No. 4,631,211, all of which are incorporated herein by reference).

The nonsupport-bound combinatorial libraries can be screened as single compounds. In addition, the nonsupport-bound combinatorial libraries can be screened as mixtures in solution in assays such as radio-receptor inhibition assays, anti-bacterial assays, anti-fungal assays, calmodulin-dependent phosphodiesterase (CaMPDE) assays and phosphodiesterase (PDE) assays, as described in detail below. Deconvolution of highly active mixtures can then be carried out by iterative or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the combinatorial libraries of the present invention using any one of the below-described assays or others well known in the art.

The iterative approach is well-known and is set forth in general in Houghten *et al.*, *Nature*, 354, 84-86 (1991) and Dooley *et al.*, *Science*, 266, 2019-2022 (1994), both of which are incorporated herein by reference. In the iterative approach, for example, sub-libraries of a molecule having three variable groups are made wherein the first variable is defined. Each of the compounds with the defined variable group is reacted with all of the other possibilities at the other two variable groups. These sub-libraries are each tested to define the identity of the second variable in the sub-library having the highest activity in the screen of choice. A new sub-library with the first two variable positions defined is reacted again with all the other possibilities at the remaining undefined variable position. As before, the identity of the third variable position in the sub-library having the highest activity is determined. If more variables exist, this process is repeated for all variables, yielding the compound with each variable contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

The positional-scanning approach has been described for various combinatorial libraries as described, for example, in R. Houghten *et al.* PCT/US91/08694 and U.S. Patent 5,556,762, both of which are incorporated herein by reference. In the positional scanning approach, sublibraries are made defining only one variable with each set of sublibraries and all possible sublibraries with each single variable defined (and all other possibilities at all of the other variable positions), made and tested. From the instant

description one skilled in the art could synthesize combinatorial libraries wherein two fixed positions are defined at a time. From the testing of each single-variable defined combinatorial library, the optimum substituent at that position can be determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the number of sublibraries for compounds with a single position defined will be the number of different substituents desired at that position, and the number of all the compounds in each sublibrary will be the product of the number of substituents at each of the other variables.

Individual compounds and pharmaceutical compositions containing the compounds, as well as methods of using the same, are included within the scope of the present invention. The compounds of the present invention can be used for a variety of purposes and indications and as medicaments for any such purposes and indications. For example, bicyclic hydantoin derivative compounds of the present invention can be used as pesticides, acaricides, receptor agonists or antagonists and antimicrobial agents, including antibacterial or antiviral agents. The libraries can be screened in any variety of melanocortin receptor and related activity assays, such as those detailed below as well as others known in the art. Additionally, the subject compounds can be useful as analgesics. Assays which can be used to test the biological activity of the instant compounds include antimicrobial assays, a competitive enzyme-linked immunoabsorbent assay and radio-receptor assays, as described below.

The melanocortin (MC) receptors are a group of cell surface proteins that mediate a variety of physiological effects, including regulation of adrenal gland function such as production of the glucocorticoids cortisol and aldosterone; control of melanocyte growth and pigment production; thermoregulation; immunomodulation; and analgesia. Five distinct MC receptors have been cloned and are expressed in a variety of tissues, including melanocytes, adrenal cortex, brain, gut, placenta, skeletal muscle, lung, spleen, thymus, bone marrow, pituitary, gonads and adipose tissue (Tatro, Neuroimmunomodulation 3:259-284 (1996)). Three MC receptors, MCR-1, MCR-3 and MCR-4, are expressed in brain tissue (Xia et al., Neuroreport 6:2193-2196 (1995)).

A variety of ligands termed melanocortins function as agonists that stimulate the activity of MC receptors. The melanocortins include melanocyte-stimulating hormones (MSH) such as α-MSH, β-MSH and γ-MSH, as well as adrenocorticotropic hormone (ACTH). Individual ligands can bind to multiple MC receptors with differing relative affinities. The variety of ligands and MC receptors with differential tissue-specific expression likely provides the molecular basis for the diverse physiological effects of melanocortins and MC receptors. For example, α-MSH antagonizes the actions of immunological substances such as cytokines and acts to modulate fever, inflammation and immune responses (Catania and Lipton, Annals N. Y. Acad. Sci. 680:412-423 (1993)).

The role of certain specific MC receptors in some of the physiological effects described above for MC receptors has been elucidated. For example, MCR-1 is

involved in pain and inflammation. MCR-1 mRNA is expressed in neutrophils (Catania et al., Peptides 17:675-679 (1996)). The anti-inflammatory agent α-MSH was found to inhibit migration of neutrophils. Thus, the presence of MCR-1 in neutrophils correlates with the anti-inflammatory activity of α-MSH.

An interesting link of MC receptors to regulation of food intake and obesity has recently been described. The brain MC receptor MCR-4 has been shown to function in the regulation of body weight and food intake. Mice in which MCR-4 has been knocked out exhibit weight gain (Huszar et al., Cell 88:131-141 (1997)). In addition, injection into brain of synthetic peptides that mimic melanocortins and bind to MCR-4 caused suppressed feeding in normal and mutant obese mice (Fan et al., Nature 385:165-168 (1997)). These results indicate that the brain MC receptor MCR-4 functions in regulating food intake and body weight.

Due to the varied physiological activities of MC receptors, high affinity ligands of MC receptors could be used to exploit the varied physiological responses of MC receptors by functioning as potential therapeutic agents or as lead compounds for the development of therapeutic agents. Furthermore, due to the effect of MC receptors on the activity of various cytokines, high affinity MC receptor ligands could also be used to regulate cytokine activity.

A variety of assays can be used to identify or characterize MC receptor ligands of the invention. For example, the ability of a bicyclic hydantoin derivative compound to compete for binding of a known MC receptor ligand can be used to assess the affinity and specificity

of a bicyclic hydantoin derivative compound for one or more MC receptors. Any MC receptor ligand can be used so long as the ligand can be labeled with a detectable moiety. The detectable moiety can be, for example, a radiolabel, fluorescent label or chromophore, or any detectable functional moiety so long as the MC receptor ligand exhibits specific MC receptor binding. A particularly useful detectable MC receptor ligand for identifying and characterizing other MC receptor ligands is ^{125}I-HP 467, which has the amino acid sequence Ac-Nle-Gln-His-(*p*(I)-D-Phe)-Arg-(D-Trp)-Gly-NH_2 and is described in Dooley et al., "Melanocortin Receptor Ligands and Methods of Using Same," U.S. patent application 09/027,108, filed February 20, 1998, which is incorporated herein by reference. HP 467 is a *para*-iodinated form of HP 228.

Using assay methods such as those described above, binding kinetics and competition with radiolabeled HP 467 can confirm that bicyclic hydantoin derivative compounds of the invention bind to one or more MC receptors. Furthermore, bicyclic hydantoin derivative compounds of the invention can exhibit a range of affinities and specificity for various MC receptors.

The invention provides MC receptor ligands that can bind to several MC receptors with similar affinity. In addition, the invention also provides MC receptor ligands that can be selective for one or more MC receptors. As used herein, the term "selective" means that the affinity of a MC receptor ligand differs between one MC receptor and another by about 10-fold, generally about 20- to 50-fold, and particularly about 100-fold. In some cases, a MC receptor ligand having broad specificity is desired. In other cases, it is desirable

to use MC receptor ligands having selectivity for a particular MC receptor. For example, MCR-1 ligands are particularly useful for treating pain and inflammation, whereas MCR-4 ligands are useful for treating obesity. The binding characteristics and specificity of a given MC receptor ligand can be selected based on the particular disease or physiological effect that is desired to be altered.

Another assay useful for identifying or characterizing MC receptor ligands measures signaling of MC receptors. MC receptors are G protein-coupled receptors that couple to adenylate cyclase and produce cAMP. Therefore, measuring cAMP production in a cell expressing a MC receptor and treated with a MC receptor ligand can be used to assess the function of the MC receptor ligand in activating a MC receptor.

Ligands for MC-3 that can alter the activity of an MC-3 receptor can be useful for treating sexual dysfunction and other conditions or conditions associated with MC-3 such as inflammation. Other MC-3-associated conditions that can be treated with the MC-3 receptor ligands include disuse deconditioning; organ damage such as organ transplantation or ischemic injury; adverse reactions associated with cancer chemotherapy; diseases such as atherosclerosis that are mediated by free radicals and nitric oxide action; bacterial endotoxic sepsis and related shock; adult respiratory distress syndrome; and autoimmune or other patho-immunogenic diseases or reactions such as allergic reactions or anaphylaxis, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, glomerulonephritis, systemic lupus erythematosus, transplant atherosclerosis and

parasitic mediated immune dysfunctions such as Chagas's disease.

The invention further provides a method for treating an MC-3-associated condition in a subject. The term "MC-3-associated condition" includes any condition or condition mediated by MC-3 or can be affected by binding an MC-3 ligand. Such conditions include inflammation and sexual dysfunction.

The term "sexual dysfunction" herein means any condition that inhibits or impairs normal sexual function, including coitus. However, the term need not be limited to physiological conditions, but may include psychogenic conditions or perceived impairment without a formal diagnosis of pathology.

In males, sexual dysfunction includes erectile dysfunction. The term "erectile dysfunction" or "impotence" means herein the inability or impaired ability to attain or sustain an erection that would be of satisfactory rigidity for coitus. Sexual dysfunction in males can also include premature ejaculation and priapism, which is a condition of prolonged and sometimes painful erection unrelated to sexual activity, often associated with sickle-cell disease.

In females, sexual dysfunction includes sexual arousal disorder. The term "sexual arousal disorder" means herein a persistent or recurrent failure to attain or maintain the lubrication-swelling response of sexual excitement until completion of sexual activity. Sexual dysfunction in females can also include inhibited orgasm and dyspareunia, which is painful or difficult coitus.

Sexual dysfunction can also be manifested as inhibited sexual desire or inhibited lordosis behavior in animals.

In addition, the ability of the compounds to inhibit bacterial growth, and therefore be useful to that infection, can be determined by methods well known in the art. Compounds of the present invention can be shown to have antimicrobial activity by the *in vitro* antimicrobial activity assay described below and, therefore, are useful as antimicrobial agents.

Moreover, an exemplary *in vitro* antimicrobial activity assay is described in Blondelle and Houghten, *Biochemistry* 30:4671-4678 (1991), which is incorporated herein by reference. In brief, *Staphylococcus aureus* ATCC 29213 (Rockville, MD) is grown overnight at 37°C in Mueller-Hinton broth, then re-inoculated and incubated at 37°C to reach the exponential phase of bacterial growth (i.e., a final bacterial suspension containing 10^5 to 5 x 10^5 colony-forming units/ml). The concentration of cells is established by plating 100 µl of the culture solution using serial dilutions (e.g., 10^{-2}, 10^{-3} and 10^{-4}) onto solid agar plates. In 96-well tissue culture plates, compounds, individual or in mixtures, are added to the bacterial suspension at concentrations derived from serial two-fold dilutions ranging from 1500 to 2.9 µg/ml. The plates are incubated overnight at 37°C and the growth determined at each concentration by OD_{620} nm. The IC_{50} (the concentration necessary to inhibit 50% of the growth of the bacteria) can then be calculated.

The competitive ELISA method which can be used here is a modification of the direct ELISA technique described previously in Appel et al., J. Immunol. 144:976-983 (1990), which is incorporated herein by

reference. It differs only in the MAb addition step. Briefly, multi-well microplates are coated with the antigenic peptide (Ac-GASPYPNLSNQQT-NH_2) at a concentration of 100 pmol/50 µl. After blocking, 25 µl of a 1.0 mg/ml solution of each mixture of a synthetic combinatorial library (or individual compound) is added, followed by MAb 125-10F3 (Appel et al., *supra*) (25 µl per well). The MAb is added at a fixed dilution in which the bicyclic guanidine in solution effectively competes for MAb binding with the antigenic peptide adsorbed to the plate. The remaining steps are the same as for direct ELISA. The concentration of compound necessary to inhibit 50% of the MAb binding to the control peptide on the plate (IC_{50}) is determined by serial dilutions of the compound.

Alternative screening can be done with radio-receptor assays. The radio-receptor assay, can be selective for any one of the µ, κ, or δ opiate receptors. Compounds of the present invention can be useful in vitro for the diagnosis of relevant opioid receptor subtypes, such as κ, in the brain and other tissue samples. Similarly, the compounds can be used *in vivo* diagnostically to localize opioid receptor subtypes.

The radio-receptor assays are also an indication of the compounds' analgesic properties as described, for example, in Dooley et al., *Proc. Natl. Acad. Sci.*, 90:10811-10815 (1993). For example, it can be envisioned that these compounds can be used for therapeutic purposes to block the peripheral effects of a centrally acting pain killer. For instance, morphine is a centrally acting pain killer. Morphine, however, has a number of deleterious effects in the periphery which are not required for the desired analgesic effects, such as

constipation and pruritus (itching). While it is known that the many compounds do not readily cross the blood-brain barrier and, therefore, elicit no central effect, the subject compounds can have value in blocking the periphery effects of morphine, such as constipation and pruritus. Accordingly, the subject compounds can also be useful as drugs, namely as analgesics, or to treat pathologies associated with other compounds which interact with the opioid receptor system.

Additionally, such compounds can be tested in a σ receptor assay. Ligands for the σ receptor can be useful as antipsychotic agents, as described in Abou-Gharbia et al., *Annual Reports in Medicinal Chemistry*, 28:1-10 (1993).

Radio-receptor assays can be performed with particulate membranes prepared using a modification of the method described in Pasternak et al., *Mol. Pharmacol.* 11:340-351 (1975), which is incorporated herein by reference. Rat brains frozen in liquid nitrogen can be obtained from Rockland (Gilbertsville, PA). The brains are thawed, the cerebella removed and the remaining tissue weighed. Each brain is individually homogenized in 40 ml Tris-HCl buffer (50 mM, pH 7.4, 4°C) and centrifuged (Sorvall® RC5C SA-600: Du Pont, Wilmington, DE) (16,000 rpm) for 10 minutes. The pellets are resuspended in fresh Tris-HCl buffer and incubated at 37°C for 40 minutes. Following incubation, the suspensions are centrifuged as before, the resulting pellets resuspended in 100 volumes of Tris buffer and the suspensions combined. Membrane suspensions are prepared and used in the same day. Protein content of the crude homogenates generally range from 0.15-0.2 mg/ml as determined using the method described in Bradford, M.M.,

Anal. Biochem. 72:248-254 (1976), which is incorporated herein by reference.

Binding assays are carried out in polypropylene tubes, each tube containing 0.5 ml of membrane suspension. 8 nM of ^{3}H-[D-Ala^2,Me-Phe^4,Gly-ol^5]enkephalin (DAMGO) (specific activity = 36 Ci/mmol, 160,000 cpm per tube; which can be obtained from Multiple Peptide Systems, San Diego, CA, through NIDA drug distribution program 271-90-7302) and 80 µg/ml of bicyclic guanidine, individual or as a mixture and Tris-HCl buffer in a total volume of 0.65 ml. Assay tubes are incubated for 60 mins. at 25°C. The reaction is terminated by filtration through GF-B filters on a Tomtec harvester (Orange, CT). The filters are subsequently washed with 6 ml of Tris-HCl buffer, 4°C. Bound radioactivity is counted on a Pharmacia Biotech Betaplate Liquid Scintillation Counter (Piscataway, NJ) and expressed in cpm. To determine inter- and intra-assay variation, standard curves in which ^{3}H-DAMGO is incubated in the presence of a range of concentrations of unlabeled DAMGO (0.13-3900 nM) are generally included in each plate of each assay (a 96-well format). Competitive inhibition assays are performed as above using serial dilutions of the bicyclic guanidines, individually or in mixtures. IC_{50} values (the concentration necessary to inhibit 50% of ^{3}H-DAMGO binding) are then calculated. IC_{50} values of less than 1000 nM are indicative of highly active opioid compounds which bind to the µ receptor, with particularly active compounds having IC_{50} values of 100 nM or less and the most active compounds with values of less than 10 nM.

As opposed to this µ receptor selective assay, which can be carried out using ^{3}H-DAMGO as radioligand, as described above, assays selective for κ receptors can be

carried out using [^{3}H]-U69,593 (3 nM, specific activity 62 Ci/mmol) as radioligand. Assays selective for δ opiate receptors can be carried out using tritiated DSLET ([D-Ser^2, D-Leu^5]-threonine-enkephalin) as radioligand. Assays selective for the σ opiate receptor can use radiolabeled pentazocine as ligand.

Screening of combinatorial libraries and compounds of the invention can be done with an anti-fungal assay. Compounds of the present invention can be useful for treating fungal infections.

Screening of combinatorial libraries and compounds of the invention also can be done with a calmodulin-dependent phosphodiesterase (CaMPDE) assay. Compounds of the present invention can be useful as calmodulin antagonists.

Calmodulin (CaM), which is the major intracellular calcium receptor, is involved in many processes that are crucial to cellular viability. In particular, calmodulin is implicated in calcium-stimulated cell proliferation. Calmodulin antagonists are, therefore, useful for treating conditions associated with increased cell proliferation, for example, cancer. In addition, calmodulin antagonists such as compounds of the subject invention are useful both in vitro and in vivo for identifying the role of calmodulin in other biological processes. The disadvantages of known antagonists such as trifluoperazine and N-(4-aminobutyl)-5-chloro-2-naphthalenesulfonamide (W13) include their non-specificity and toxicity. In contrast, advantages of the combinatorial libraries and compounds of the subject invention as calmodulin antagonists include their reduced flexibility and ability to generate broader

conformational space of interactive residues as compared to their linear counterparts.

An example of an assay that identifies CaM antagonists is a CaMPDE assay. In brief, samples are mixed with 50 µl of assay buffer (360 mM Tris, 360 mM Imidazole, 45 mM $Mg(CH_3COO)_2$, pH 7.5) and 10 µl of $CaCl_2$ (4.5 mM) to a final volume of 251 µl. 25 µl of calmodulin stock solution (Boehringer Mannheim; 0.01 µg/µl) is then added and the samples then sit at room temperature for 10 minutes. 14 µl of PDE (Sigma; 2 Units dissolved in 4 ml of water; stock concentration: 0.0005 Units/µl) is then added, followed by 50 µl of 5'-nucleotidase (Sigma; 100 Units dissolved in 10 ml of 10 mM Tris-HCl containing 0.5 mM $Mg(CH_3COO)_2$, pH 7.0; stock concentration: 10 Units/ml). The samples are then incubated for 10 minutes at 30°C. 50 µl of adenosine 3',5'-cyclic monophosphate (cAMP) (20 mM in water at pH 7.0) is added, the samples incubated for 1 hour at 30°C and then vortexed. 200 µl of trichloroacetic acid (TCA) (55% in water) is added to a 200 µl sample aliquot, which is then vortexed and centrifuged for 10 minutes. 80 µl of the resulting supernatants of each sample is transferred to a 96-well plate, with 2 wells each containing 80 µl of each sample. 80 µl of ammonium molybdate (1.1% in 1.1N H_2SO_4) is then added to all the wells, and the OD of each were determined at 730nm, with the values later subtracted to the final OD reading. 16 µl of reducing agent (6g sodium bisulfite, 0.6g sodium sulfite and 125mg of 1-amino-2-naphtol-4-sulfonic acid in 50ml of water) is then added to one of each sample duplicate and 16 µl of water is added to the other duplicate. After sitting for 1 hour at room temperature, the OD of each well is determined at 730nm. The percent inhibition of calmodulin activity is then calculated for

each sample, using as 0% inhibition a control sample containing all reagents without any test samples and as 100% inhibition a control sample containing test samples and all reagents except calmodulin. In addition, the percent inhibition of phosphodiesterase activity was determined by following a similar protocol as the CaMPDE assay described above, except not adding calmodulin to the sample mixture and calculating the percent inhibition by using as 0% inhibition a control reagent without any test samples and as 100% inhibition a control sample containing test samples and all reagents except cAMP.

The following examples are provided to illustrate but not limit the present invention. The following abreviations have the corresponding meanings:

MBHA : 4-methylbenzhydrylamine;
DMF : N,N-dimethylforamide;
HOBt : 1-hydroxybenzotriazole;
DMSO : dimethylsulfoxide;
Boc : tert-butoxycarbonyl;
FMOC : 9-fluorenyl-methoxycarbonyl;
DMAP : 4-dimethylamino-pyridine;
DIC : N,N'-diisopropylcarbodiimide;
TFA : trifluoroacetic acid;
DIEA : N,N-diisopropylethylamine;
DCM : dichloromethane;
TMOF: trimethylorthoformate;
HATU : azabenzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate;
CDI : carbonyldiimidazole
NMP : N-methylpyrrolidinone
DMA : N,N-dimethyl acetamide
RT : room temperature
IPA : isopropyl alcohol

MeOH: methanol
MeOEtOH : 2-methoxyethanol
DCE : 1,2-dichloroethane
THF : tetrahydrofuran
ACN : acetonitrile
Wang resin : *p*-benzyloxybenzyl alcohol-polystyrene
Br-Wang resin : *p*-benzyloxybenzyl bromide-polystyrene
PP : polypropylene
PPh3Br2 : triphenylphosphine dibromide
DMAP : 4-dimethylamino-pyridine
KOtBu : potassium tert-butoxide
NaOMe : sodium methoxide
BtCH2CN : 1-(cyanomethyl)benzotriazole
DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene
Boc : tertbutoxycarbonyl;
AcOH : acetic acid
HPLC/MS : high performance liquid chromatography - mass spectrometry;
FIA-MS : flow injection analysis - mass spectrometry
ELSD : evaporative light scattering detector
THB : Todd Hewitt Broth
OD : optical density

Example 1

Preparation of Bicyclic Hydantoins

Step a: Coupling of N-Boc-amino acid to MBHA and Boc deprotection.

MBHA-HCl resin (methylbenzhydrylamine hydrochloride) (1.6 g, 2.34 mmol NH_2) was dispensed into a porous polypropylene packet (Tea-bag, 75mm x 80mm, 65µ). The resin in the packet was neutralized with 5% DIEA/DCM (3X80 mL) and then washed with DCM (80 mL). The packet

was put in a Nalgene bottle and DMF (78 mL), Boc-L-phenylalanine (6.18 g, 23.3 mmol), DIEA (3.01 g, 23.3 mmol), HOBT (2.62 g, 19.4 mmol) and DIC (2.94 g, 23.3 mmol) were added sequentially. After shaking the bottle for 20 hours, the packet was washed with DMF (3X80 mL), DCM (3X80 mL) and MeOH (3X80 mL) and dried in air for overnight. The packet was shaken with 55% TFA/DCM (80 mL) at room temperature for 30 minutes. It was then washed with DCM (3X80 mL), 5% DIEA/DCM (3X80 mL) and MeOH (2X80 mL) and dried in air for overnight.

The following protected amino acids were coupled to resin according to the above-described procedures:

BOC-L-PHENYLALANINE
BOC-L-ALANINE
BOC-L-2-AMINOBUTYRIC ACID
BOC-4-AMINOBUTYRIC ACID
BOC-6-AMINOHEXANOIC ACID
BOC-4-CHLORO-L-PHENYLALANINE
BOC-L-METHIONINE
BOC-O-METHYL-L-TYROSINE
BOC-L-VALINE
N^{a}-BOC-N^{im}-TOSYL-L-HISTIDINE
BOC-O-BENZYL-L-SERINE
BOC-L-LEUCINE
BOC-3-CYCLOHEXYL-L-ALANINE
4-(BOC-AMINOMETHYL)BENZOIC ACID
4-(BOC-AMINOMETHYL)CYCLOHEXANECARBOXYLIC ACID

Step b: Sulfonylation of amine with sulfonyl chloride.

The packet from step a was shaken with a solution of DIEA (2.89 g, 22.4 mmol), 2-thiophene sulfonyl chloride (3.41 g, 18.69 mmol) in DCM (75 mL) for 48 hours until

ninhydrin Kaiser test of a few resin beads taken from the packet was negative. The packet was washed thoroughly with DCM (3X80 mL), DMF (3X80 mL) and t-butylmethyl ether (3X80 mL), then dried in air overnight. The following sulfonyl chlorides were also added according to the procedure of step b:

2-THIOPHENESULFONYL CHLORIDE
BENZENESULFONYL CHLORIDE
2,5-DICHLOROBENZENESULFONYL CHLORIDE
2-NITROBENZENESULFONYL CHLORIDE
4-BROMOBENZENESULFONYL CHLORIDE
4-FLUOROBENZENESULFONYL CHLORIDE
4-CHLOROBENZENESULFONYL CHLORIDE
3-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
3,4-DICHLOROBENZENESULFONYL CHLORIDE
3-CHLORO-4-FLUOROBENZENESULFONYL CHLORIDE
2-FLUOROBENZENESULFONYL CHLORIDE
3-FLUOROBENZENESULFONYL CHLORIDE
4-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
2,4-DIFLUOROBENZENESULFONYL CHLORIDE
2-CHLOROBENZENESULFONYL CHLORIDE
2-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
3-CHLOROBENZENESULFONYL CHLORIDE
3,5-DICHLOROBENZENESULFONYL CHLORIDE
2,3-DICHLOROBENZENESULFONYL CHLORIDE
2-BROMOBENZENESULFONYL CHLORIDE
5-(2-PYRIDYL)THIOPHENE-2-SULFONYL CHLORIDE
2-CHLORO-5-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
4-CYANOBENZENESULFONYL CHLORIDE
2-CYANOBENZENESULFONYL CHLORIDE
5-CHLORO-1,3-DIMETHYLPYRAZOLE-4-SULPHONYL CHLORIDE
3,5-DIMETHYLISOXAZOLE-4-SULFONYL CHLORIDE
2,4-DICHLOROBENZENESULFONYL CHLORIDE
2-CHLORO-4-(TRIFLUOROMETHYLBENZENE)SULFONYL CHLORIDE

2-CHLORO-4-FLUOROBENZENESULFONYL CHLORIDE
2,4,6-TRICHLOROBENZENESULFONYL CHLORIDE
1-METHYLIMIDAZOLE-4-SULPHONYL CHLORIDE
METHYL 3-CHLOROSULFONYLTHIOPHENE-2-CARBOXYLATE
5-ISOXAZOL-3-YLTHIOPHENE-2-SULFONYL CHLORIDE
4-BIPHENYLSULFONYL CHLORIDE
3,4-DIFLUOROBENZENESULPHONYL CHLORIDE
3-METHYL-5-CHLORO-2-BENZOTHIOPHENE
3-CYANOBENZENESULPHONYL CHLORIDE
4-METHYLSULFONYLBENZENESULFONYL CHLORIDE
2-METHYLSULFONYLBENZENESULFONYL CHLORIDE

Step c: Formation of 4-aminoproline derivative on resin via the Mitsunobu reaction and Boc deprotection.

The packet from step b was shaken in a glass bottle with a 0.35 M solution of *trans*-L-4-hydroxyproline methyl ester (4.58 g, 18.69 mmol), triphenylphosphine (4.90 g, 18.69 mmol), NMM (N-methylmorpholine) (17.8 mL), THF (17.8 mL) and DCM (17.8 mL) for 5 minutes. The mixture was then cooled to 0-5° C for 2 hours in a refrigerator. The glass bottle was then equipped with a thermometer, an additional funnel, a nitrogen stream inlet, an ice water bath and an electric shaker. A solution of DIAD (diisopropyl azodicarboxylate) (3.78 g, 18.69 mmol) in DCM (5 mL) was added dropwise under nitrogen atmosphere while the bottle was shaken. The reaction mixture was maintained at 0-5° C with an ice water bath during the addition of DIAD. The reaction mixture was then shaken at room temperature for 3 days. The packet was then washed thoroughly with DMF (3X80 mL), DCM (3X80 mL) and MeOH (3X80 mL) and dried in air overnight. The packet was shaken with 55% TFA/DCM (80 mL) at room temperature for 30 minutes and washed with DCM (3X80 mL), 5% DIEA/DCM (3X80 mL) and MeOH (3X80 mL) and dried in air overnight.

Step d: Reaction of isocyanate to form urea.

The resin was removed from the packet and suspended in DMF (20 mL) and the resin suspension was distributed equally into 40 wells of a microtiter plate (2 mL X 40). The extra DMF was removed from the wells, leaving about 0.2 mL of DMF in each well. An array of 40 different isocyanate solutions (0.5 M in DMF) was prepared. To each well was added 1.0 mL of the following isocyanate in solution:

PHENYL ISOCYANATE
2-BROMOPHENYL ISOCYANATE
2-FLUOROPHENYL ISOCYANATE
2,4-DIFLUOROPHENYL ISOCYANATE
2,6-DIFLUOROPHENYL ISOCYANATE
2-CHLOROPHENYL ISOCYANATE
2,4-DICHLOROPHENYL ISOCYANATE
2,5-DICHLOROPHENYL ISOCYANATE
2-METHOXYPHENYL ISOCYANATE
O-TOLYL ISOCYANATE
2-ETHYLPHENYL ISOCYANATE
3-FLUOROPHENYL ISOCYANATE
3-CHLOROPHENYL ISOCYANATE
3-METHOXYPHENYL ISOCYANATE
M-TOLYL ISOCYANATE
4-BROMOPHENYL ISOCYANATE
4-FLUOROPHENYL ISOCYANATE
4-METHOXYPHENYL ISOCYANATE
P-TOLYL ISOCYANATE
1-NAPHTHYL ISOCYANATE
BENZYL ISOCYANATE
2-ISOPROPYLPHENYL ISOCYANATE
2,4-DIMETHYLPHENYL ISOCYANATE

2,5-DIMETHYLPHENYL ISOCYANATE
2-ETHYL-6-METHYLPHENYL ISOCYANATE
3-(METHYLTHIO)PHENYL ISOCYANATE
3,4-DIMETHYLPHENYL ISOCYANATE
3,5-DIMETHYLPHENYL ISOCYANATE
2-METHOXY-5-METHYLPHENYL ISOCYANATE
3-ETHYLPHENYL ISOCYANATE
4-ETHOXYPHENYL ISOCYANATE
4-(METHYLTHIO)PHENYL ISOCYANATE
4-ISOPROPYLPHENYL ISOCYANATE
4-ETHYLPHENYL ISOCYANATE
4-N-BUTYLPHENYL ISOCYANATE
2-ISOPROPYL-6-METHYLPHENYL ISOCYANATE
2,4,5-TRIMETHYLPHENYL ISOCYANATE
4-BUTOXYPHENYL ISOCYANATE
5-FLUORO-2-METHYLPHENYL ISOCYANATE
4-(DIMETHYLAMINO)PHENYL ISOCYANATE

The plate was capped tightly and shaken at room temperature for 3 d. The resin was washed with DMF (3X1mL/well), MeOH (3X1mL/well) and DMF(3X1mL/well). The extra DMF was removed, leaving about 0.2 mL of DMF in each well.

Step e: Tetramethylguanidine-mediated cyclization to bicyclic hydantoin.

To each well of the microtiter plate was added 1.1 mL of 0.025 M TMG (tetramethyl guanidine). The plate was capped and shaken at room temperature for 16 h. The resin was washed with DMF (3X1mL/well), MeOH (3X1mL/well), DMF (3X1mL/well), MeOH (6X1mL/well). The resin was dried in air for three days and under vacuum for overnight. The plate was treated with gaseous HF at room temperature for 2 hours. The HF was removed

completely by a stream of nitrogen and then by vacuum. The resin was extracted with acetic acid (3X0.5 mL/well). The extract was lyophilized to give the title compounds.

A library of about 8,000 individual bicyclic hydantoins was synthesized using 15 amino acids (R1), 39 sulfonyl chlorides (R2) and 40 isocyanates (R3), as listed above. All compounds were analyzed using FIA-MS.

Example 2

Anti-microbial Screen

Streptococcus pyogenes (ATCC# 97-03 14289) was grown in Todd Hewitt Broth (THB) (Difco Laboratories #0492-17-6) overnight until reaching an optical density of (OD = 0.636@ 570 nm) by reading 0.1 ml in a 96 well microtiter plate in a Molecular Devices Thermomax. This preparation was kept frozen as stocks in 30% v/v glycerol in 1.5 ml aliquots at -70^{m}C until use. Prior to experiments, 6 ml aliquots were thawed and diluted into 50 ml 2X THB. 60 ul of this dilution was added to 92 wells of microtiter plate. To three wells THB (200 ul) was added to serve as a blank and a sterility control. Test compounds in DMSO and appropriate concentrations of DMSO were added to Growth/Solvent Controls at 0 time. Plates were read at 0 time at 570 nm in the Molecular Devices plate reader to obtain compounds correction factors for insoluble or colored compounds. Plates were read again at 4 hours.

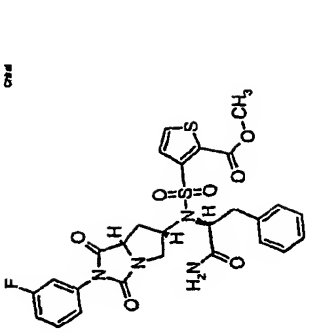
Percent inhibition is calculated with the following formulae:

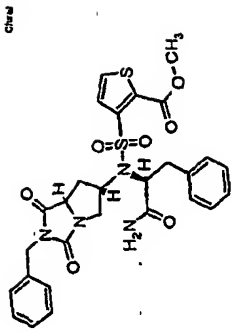
Color correct =
(O.D. 0 hr - Blank 0 hr)-(Solvent Control 0hr - Blank 0 hr)

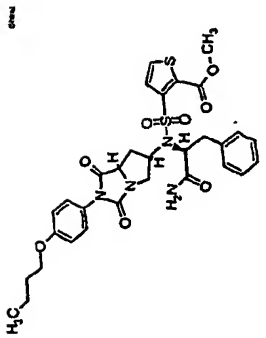
% Inhibition =
100 - $\frac{\text{O.D. test compound 4 hr - Blank 4 hr - color correct}}{\text{O.D. growth/solvent control 4 hr - Blank 4 hr}}$

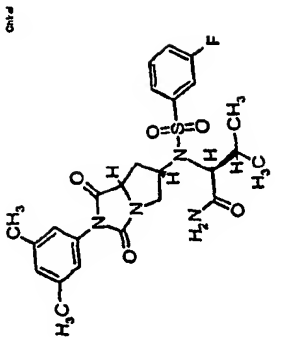
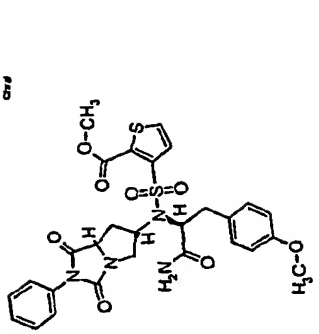
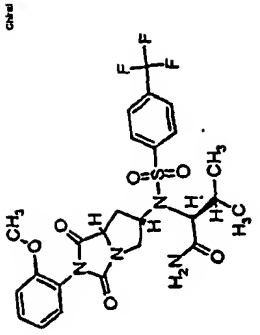
Under this formula, the most active compounds tested were as follows:

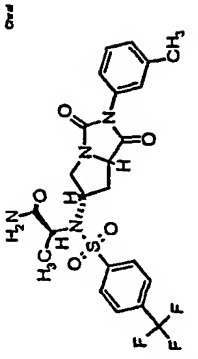
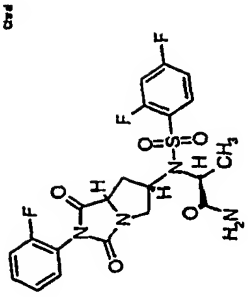
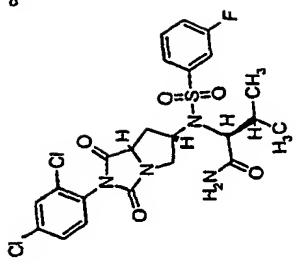
Library	Cmpd	Lot	ExtReg	Plate	Well	Raw Data	Assay Result	Assay	Conc mg/ml
8600	1052	1	000554416	8600-014	D 03	0,304	40,00	Spy4H	0,1818
8600	1061	1	000554425	8600-014	E 04	0,306	40,00	Spy4H	0,1818
8600	1078	1	000554442	8600-014	F 06	0,49	40,00	Spy4H	0,1818

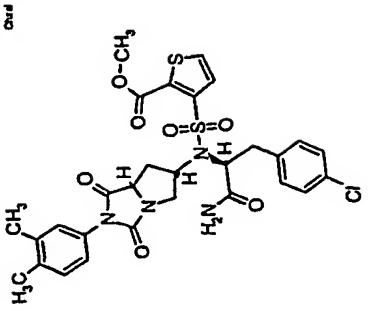
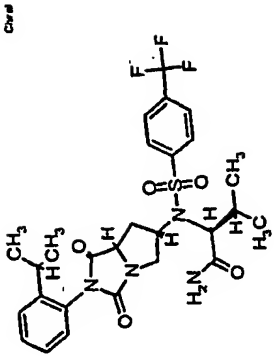
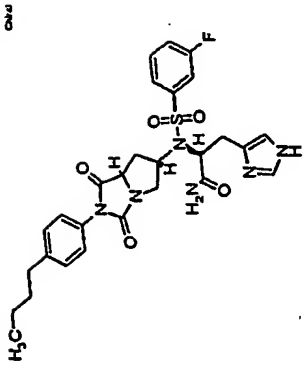




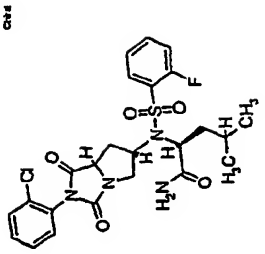
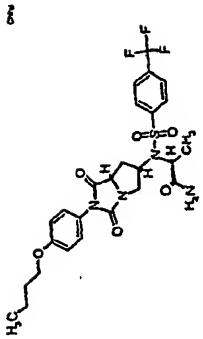
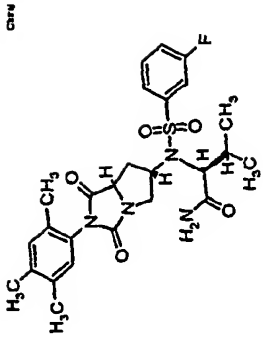


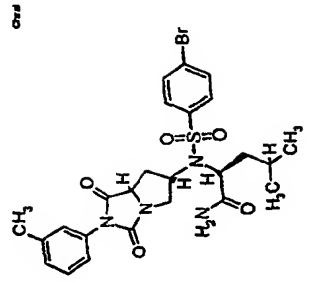
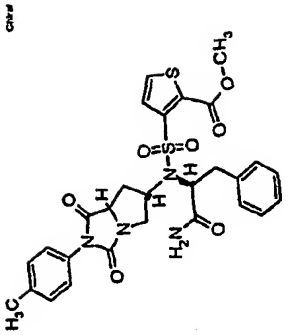
8600	1508 1	000554872	8600-019	D 10	0,305	40,07 Spy4H	0,1818	554872	
8600	241 1	000553605	8600-004	A 02	0,342	40,20 Spy4H	0,1818	553605	
8600	289 1	000553653	8600-004	A 08	0,33	40,20 Spy4H	0,1818	553653	

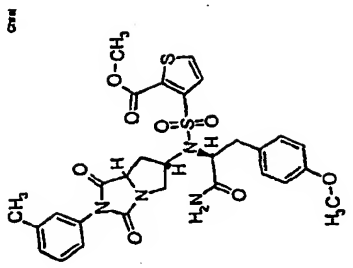
Cmd									
8600	1095 1	000554459	8600-014	G 08	0,33	40,26 Spy4H	0,1818	554459	
Cmd									
8600	7723 1	000561087	8600-097	C 07	0,273	40,49 Spy4H	0,1818	561087	
Cmd									
8600	1487 1	000554851	8600-019	G 07	0,288	40,60 Spy4H	0,1818	554851	

8600	2467 1	00055831	8600-031	C 10	0,381	40,65 Spy4H	0,1818	555831	
8600	302 1	00053666	8600-004	F 09	0,336	40,71 Spy4H	0,1818	553666	
8600	6875 1	00560239	8600-086	C 11	0,269	40,72 Spy4H	0,1818	560239	

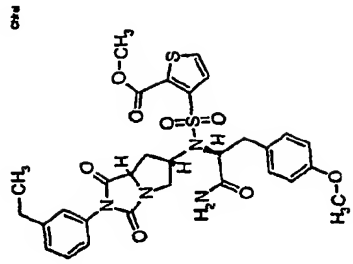
8600	2386 1	00055750	8600-030	B 10	0,333	41,43 Spy4H	0,1818	555750	
8600	7117 1	00056048	8600-089	E 11	0,343	41,43 Spy4H	0,1818	560481	
8600	1581 1	00055494	8600-020	E 09	0,291	41,76 Spy4H	0,1818	554945	

8600	7686 1	000561050	8600-097	F 02	0,309	41,81 Spy4H	0,1818	561050	
8600	1118 1	000554482	8600-014	F 11	0,293	41,82 Spy4H	0,1818	554482	
8600	1517 1	000554881	8600-019	E 11	0,329	41,91 Spy4H	0,1818	554881	

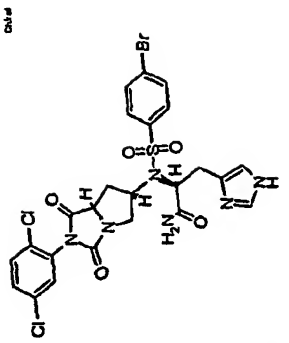
8600	7095 1	000560459	8600-089	G 08	0,332	41,97 Spy4H	0,1818	560459		
8600	1059 1	000554423	8600-014	C 04	0,363	42,35 Spy4H	0,1818	554423		



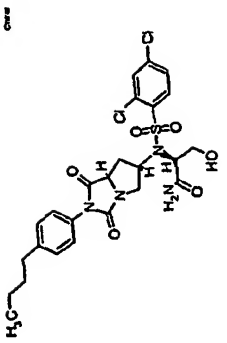
8600	255 1	000553619	8600-004	G 03	0,362	42,50	Spy4H	0,1818	553619



8600	270 1	000553634	8600-004	F 05	0,362	42,50	Spy4H	0,1818	553634



8600	6048 1	000559412	8600-076	H 07	0,273	42,53 Spy4H	0,1818	559412



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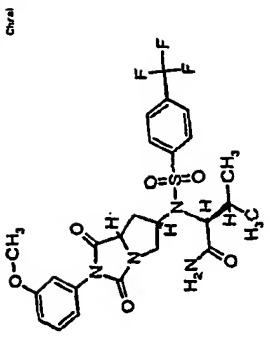
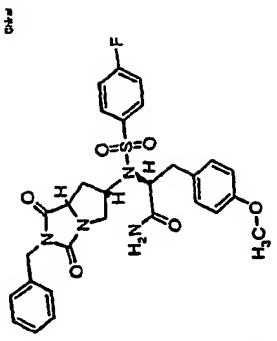
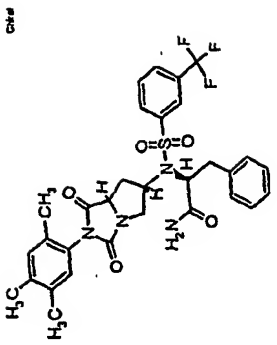
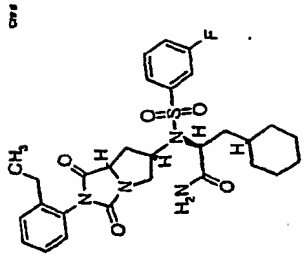
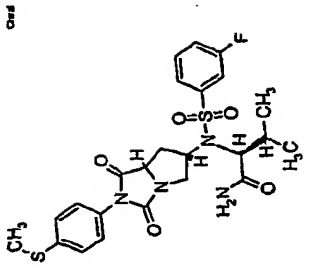
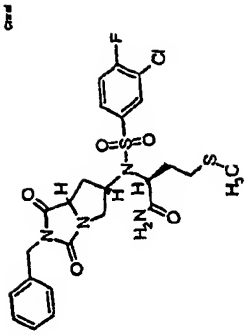
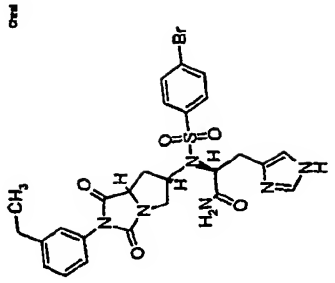
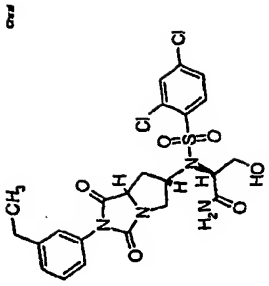
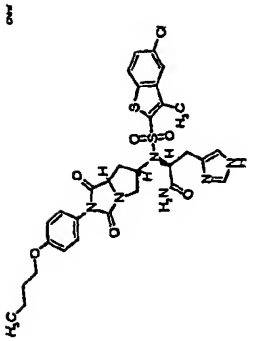
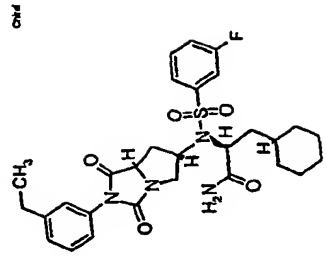
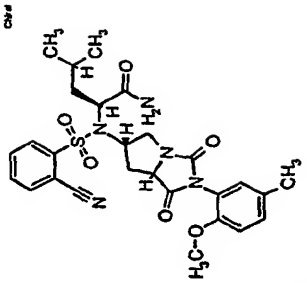


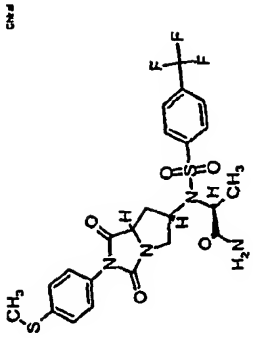
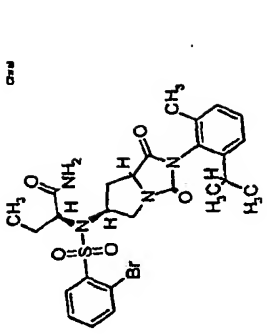
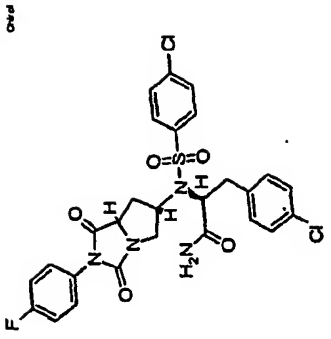
8600	294 1	000553658	8600-004	F 08	0,307	43,02 Spy4H	0,1818	553658

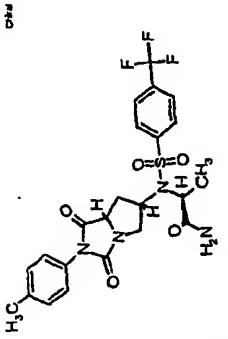
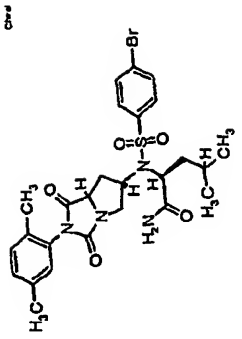
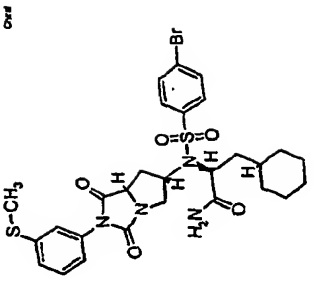
	8600	1821 1	00055185	8600-023	E 09	0,342	43,05	Spy4H	0,1818	555185
	8600	8277 1	00561641	8600-104	E 06	0,271	43,06	Spy4H	0,1818	561641
	8600	2371 1	00555735	8600-030	C 08	0,293	43,17	Spy4H	0,1818	555735

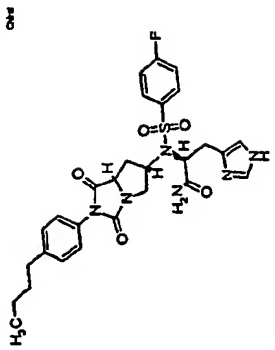
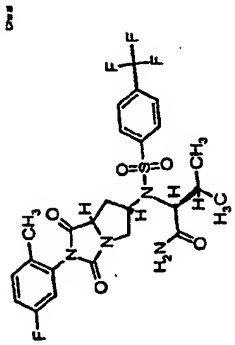
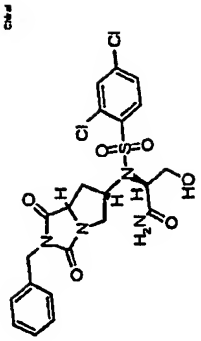
8600	1512 1	000554876	8600-019	H 10	0,471	43,23 Spy4H	0,1818	554876		
8600	941 1	000554305	8600-012	E 09	0,325	43,27 Spy4H	0,1818	554305		

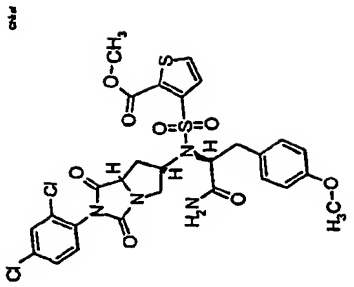
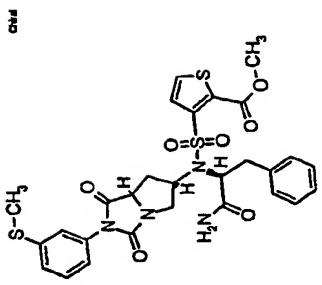
8600	6070 1	000559434	8600-076	F 10	0,262	43,37	Spy4H	0,1818	559434	
8600	590 1	000553954	8600-008	F 05	0,472	43,55	Spy4H	0,1818	553954	
8600	2838 1	000556202	8600-036	F 06	0,29	44,29	Spy4H	0,1818	556202	

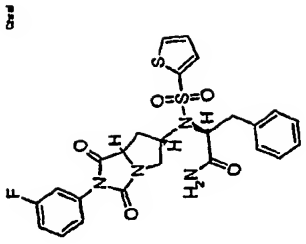
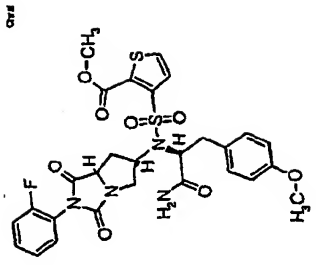
8600	2390 1	000555754	8600-030	F 10	0,295	44,33 Spy4H	0,1818	555754	
8600	5909 1	000559273	8600-074	E 10	0,299	45,05 Spy4H	0,1818	559273	

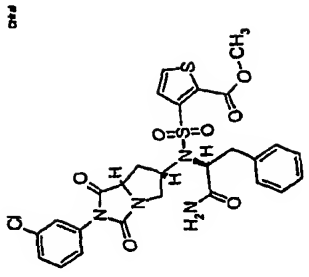
8600	1112 1	000554476	8600-014	H 10	0,451	45,21 Spy4H	0,1818	554476	
8600	8316 1	000561680	8600-104	D 11	0,502	45,82 Spy4H	0,1818	561680	
8600	897 1	000554261	8600-012	A 04	0,306	45,94 Spy4H	0,1818	554261	

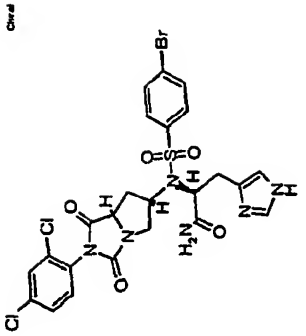
8600	1099 1	000554463	8600-014	C 09	0,312	46,78 Spy4H	0,1818	554463	
8600	7104 1	000560468	8600-089	H 09	0,419	47,01 Spy4H	0,1818	560468	
8600	1586 1	000554950	8600-020	B 10	0,42	47,05 Spy4H	0,1818	554950	

	8600	7675 1	00056103 9	8600-096	C 11	0,255	47,13 Spy4H	0,1818	561039	
	8600	319 1	00055368 3	8600-004	G 11	0,348	47,89 Spy4H	0,1818	553683	
	8600	581 1	00055394 5	8600-008	E 04	0,522	47,89 Spy4H	0,1818	553945	

8600	247 1	00055361 1	8600-004	G 02	0,354	48,40	Spy4H	0,1818	553611		
8600	1066 1	00055443 0	8600-014	B 05	0,683	49,38	Spy4H	0,1818	554430		

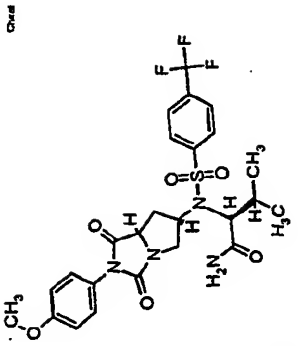
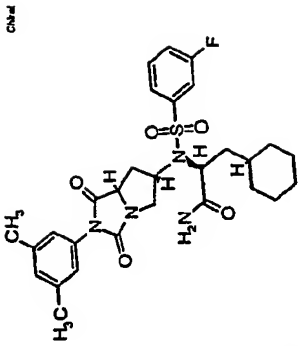
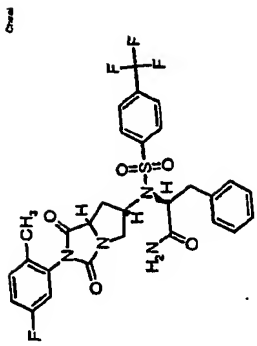
8600	2412 1	000555776	8600-031	D 03	0,694	49,76 Spy4H	0,1818	555776		
8600	243 1	000553607	8600-004	C 02	0,46	51,22 Spy4H	0,1818	553607		

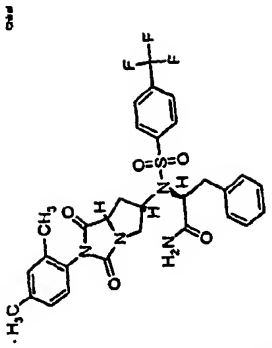




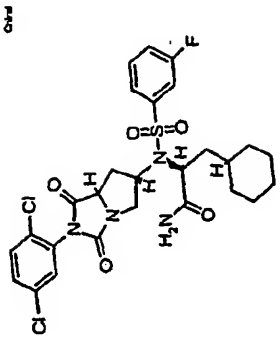
8600	1053 1	000554417	8600-014	E 03	0,386	55,37	Spy4H	0,1818	554417		
8600	6047 1	000559411	8600-076	G 07	0,239	56,31	Spy4H	0,1818	559411		

8600	2035 1	000555399	8600-026	C 06	0,232	57,39 Spy4H	0,1818	555399		
8600	1424 1	000554788	8600-018	H 09	0,354	59,87 Spy4H	0,1818	554788		
8600	598 1	000553962	8600-008	F 06	0,386	59,94 Spy4H	0,1818	553962		

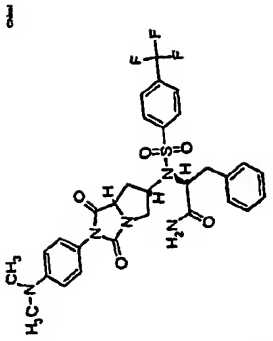
8600	298 1	000553662	8600-004	B 09	0,281	60,44 Spy4H	0,1818	553662	
8600	2388 1	000555752	8600-030	D 10	0,479	60,57 Spy4H	0,1818	555752	
8600	5879 1	000559243	8600-074	G 06	0,31	61,98 Spy4H	0,1818	559243	



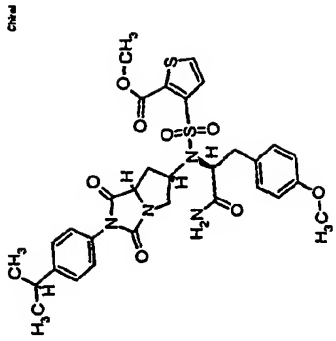
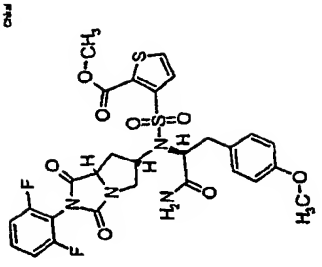
8600	5863 1	000559227	8600-074	G 04	0,342		66,81	Spy4H	0,1818	559227

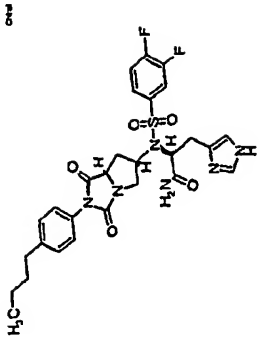
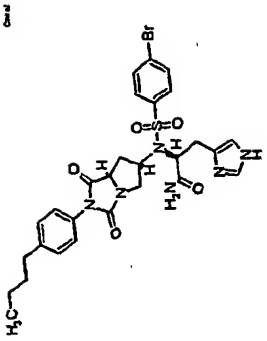
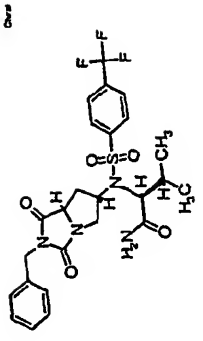


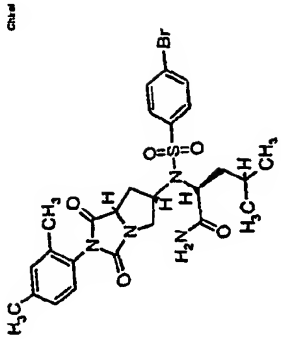
8600	2368 1	000555732	8600-030	H 07	0,322		67,23	Spy4H	0,1818	555732

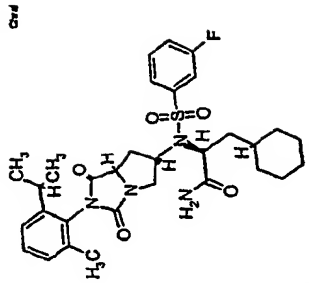


8600	5880 1	000559244	8600-074	H 06	0,427		68,16	Spy4H	0,1818	559244

8600	273 1	000553637	8600-004	A 06	0,639	68,39 Spy4H	0,1818	553637		
8600	245 1	000553609	8600-004	E 02	0,341	70,18 Spy4H	0,1818	553609		

	8600	6835 1	000560199	8600-086	C 06	0,214	70,63 Spy4H	0,1818	560199	
	8600	6075 1	000559439	8600-076	C 11	0,259	74,02 Spy4H	0,1818	559439	
	8600	301 1	000553665	8600-004	E 09	0,396	75,3 Spy4H	0,1818	553665	





8600	7103 1	000560467	8600-089	G 09	0,343	78,35 Spy4H	0,1818	560467	
8600	2396 1	000555760	8600-030	D 11	0,349	82,31 Spy4H	0,1818	555760	

EXAMPLE 3

Melanocortin Receptor Assay

This example describes methods for assaying binding to MC receptors.

All cell culture media and reagents are obtained from GibcoBRL (Gaithersburg MD), except for COSMIC CALF SERUM (HyClone; Logan UT). HEK 293 cell lines are transfected with the human MC receptors hMCR-1, hMCR-3, and hMCR-4 (Gantz et al., Biochem. Biophys. Res. Comm. 200:1214-1220 (1994); Gantz et al., J. Biol. Chem. 268:8246-8250 (1993); Gantz et al. J. Biol. Chem. 268:15174-15179 (1993); Haskell-Leuvano et al., Biochem. Biophys. Res. Comm. 204:1137-1142 (1994); each of which is incorporated herein by reference). Vectors for construction of an hMCR-5 expressing cell line are obtained, and a line of HEK 293 cells expressing hMCR-5 is constructed (Gantz, *supra*, 1994). hMCR-5 has been described previously (Franberg et al., Biochem. Biophys. Res. Commun. 236:489-492 (1997); Chowdhary et al., Cytogenet. Cell Genet. 68:1-2 (1995); Chowdhary et al., Cytogenet. Cell Genet. 68:79-81 (1995), each of which is incorporated herein by reference). HEK 293 cells are maintained in DMEM, 25 mM HEPES, 2 mM glutamine, non-essential amino acids, vitamins, sodium pyruvate, 10% COSMIC CALF SERUM, 100 units/ml penicillin, 100 µg/ml streptomycin and 0.2 mg/ml G418 to maintain selection.

Before assaying, cells are washed once with phosphate buffered saline ("PBS"; without Ca^{2+} and Mg^{2+}), and stripped from the flasks using 0.25% trypsin and 0.5 mM EDTA. Cells are suspended in PBS, 10% COSMIC CALF

SERUM and 1 mM $CaCl_2$. Cell suspensions are prepared at a density of $2x10^4$ cells/ml for HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, and $1x10^5$ cells/ml for HEK 293 cells expressing hMCR-1. Suspensions are placed in a water bath and allowed to warm to 37°C for 1 hr.

Binding assays are performed in a total volume of 250 µl for HEK 293 cells. Control and test compounds are dissolved in distilled water. ^{125}I-HP 467 (50,000 dpm) (2000 Ci/mmol) (custom labeled by Amersham; Arlington Heights IL) is prepared in 50 mM Tris, pH 7.4, 2 mg/ml BSA, 10 mM $CaCl_2$, 5 mM $MgCl_2$, 2 mM EDTA and added to each tube. To each tube is added $4x10^3$ HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, or $2x10^4$ cells expressing hMCR-1. Assays are incubated for 2.5 hr at 37°C.

GF/B filter plates are prepared by soaking for at least one hour in 5 mg/ml BSA and 10 mM $CaCl_2$. Assays are filtered using a Brandel 96-well cell harvester (Brandel Inc.; Gaithersburg, MD). The filters are washed four times with cold 50 mM Tris, pH 7.4, and the filter plates dehydrated for 2 hr and 35 µl of MICROSCINT is added to each well. Filter plates are counted using a Packard Topcount (Packard Instrument Co.) and data analyzed using GraphPad PRISM v2.0 (GraphPad Software Inc.; San Diego CA) and Microsoft EXCEL v5.0a (Microsoft Corp.; Redmond WA).

To assay bicyclic hydantoin derivative compounds, binding assays are performed in duplicate in a 96 well format. HP 467 is prepared in 50 mM Tris, pH 7.4, and ^{125}I-HP 467 is diluted to give 100,000 dpm per 50 µl. A bicyclic hydantoin derivative compound,

is added to the well in 25 µl aliquots. A 25 µl aliquot of ^{125}I-HP 467 is added to each well. A 0.2 ml aliquot of suspended cells is added to each well to give the cell numbers indicate above, and the cells are incubated at 37°C for 2.5 hr. Cells are harvested on GF/B filter plates as described above and counted.

EXAMPLE 4

Penile erection due to administration of a bicyclic hydantoin derivative compound

Adult male rats are housed 2-3 per cage and are acclimated to the standard vivarium light cycle (12 hr. light, 12 hr. dark), rat chow and water for a least a week prior to testing. All experiments are performed between 9 a.m. and noon and rats are placed in cylindrical, clear plexiglass chambers during the 60 minute observation period. Mirrors are positioned below and to the sides of the chambers, to improve viewing.

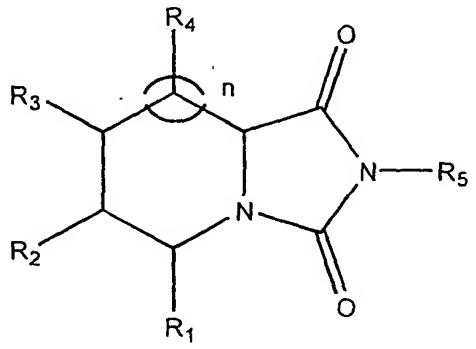
Observations begin 10 minutes after an unstraperitoneal injection of either saline or compound. An observer counts the number of grooming motions, stretches, yawns and penile erections (spontaneously occurring, not elicited by genital grooming) and records them every 5 minutes, for a total of 60 minutes. The observer is unaware of the treatment and animals are tested once, with n=6 in each group. Values in the figures represent the group mean and standard error of the mean. HP 228 can be used as a positive control for penile erections. Significant differences between groups are determined by an overall analysis of variance and the Student Neunmann-Keuls post hoc test can be used to identify individual differences between groups

($p \leq 0.05$).

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made by those skilled in the art without departing from the invention. Accordingly, the invention is set out in the following claims.

WE CLAIM:

1. A combinatorial library of two or more compounds of the formula:



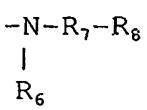
wherein:

n is 0, 1 or 2;

a) R_1; b) when n is 0, R_3; c) when n is 1, R_4 and one of R_2 and R_3; and d) when n is 2 an addition radical between R_3 and R_4, R_{34}, is present and, when n is 2, R_4 and two of R_2, R_3 and R_{34}:

are each independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, carboxy and protected carboxy; and

a) when n is 0, R_2; b) when n is 1, one of R_2 and R_3; and c) when n is 2 one of R_2, R_3 and $R_{3'}$:
is selected from the group consisting of amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino and the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is selected from the group consisting of -C(O)-, -C(O)O- and $-S(O)_2-$ and M is selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_7 is the formula -D-W-E-, wherein at least one of D, W and E is present and the other two are optionally present or absent, and wherein:
W is selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene; and D, which, if present, is

directly attached to the nitrogen depicted in the formula, and E are independently selected from the group consisting of C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene and C_2 to C_{12} substituted alkynylene;

R_8 is selected from the group consisting of a hydrogen atom, a halide, $-OR_9$, $-CO_2R_9$, $-C(O)NR_9R_{10}$ and $-NR_9R_{10}$, wherein R_9 and R_{10} are independently selected from the group consisting of a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl; and

R_5 is selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl,

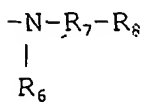
naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, heterocyclic ring and substituted heterocyclic ring, or the group consisting of (i) the formula $-C(O)R_{11}$; (ii) the formula $-C(O)OR_{11}$; (iii) the formula $-C(O)NHR_{11}$; (iv) the formula $-C(O)NR_{11}R_{12}$; and (v) the formula $-S(O_2)R_{11}$, wherein R_{11} and R_{12} are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, heterocyclic ring and substituted heterocyclic ring, or R_5, together with the adjoining nitrogen atom depicted in the formula, form a heterocyclic ring or substituted heterocyclic ring, wherein said ring is non-aromatic.

2. The combinatorial library of claim 1, wherein n is 0.

3. The combinatorial library of claim 2, wherein R_1 and R_3 are each a hydrogen atom.

4. The combinatorial library of claim 2, wherein

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of a phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl and substituted heteroaryl;

R_7 is the formula -D-W-, wherein D is present and W is optionally present or absent, and wherein:
D is selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and W is selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, arylene and substituted arylene; and

R_8 is $-C(O)NR_9R_{10}$, wherein one of R_9 and R_{10} is selected from the group consisting of a functionalized resin and a hydrogen atom, and the other is a hydrogen atom.

5. The combinatorial library of claim 1, wherein

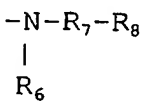
R_5 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl and C_7 to C_{19} substituted phenylalkyl.

6. The combinatorial library of claim 1, wherein:

n is 0;

R_1 and R_3 are each a hydrogen atom;

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl and substituted heteroaryl;

R_7 is the formula -D-W-, wherein D is present and W is optionally absent or present, and wherein:
D is selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and W is selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, arylene and substituted arylene; and

R_8 is $-C(O)NR_9R_{10}$, wherein one of R_9 and R_{10} is selected from the group consisting of a

functionalized resin and a hydrogen atom, and the other is a hydrogen atom; and

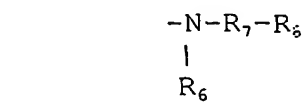
R_5 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl and C_7 to C_{18} substituted phenylalkyl.

7. The combinatorial library of claim 1, wherein:

n is 0;

R_1 and R_3 are each a hydrogen atom;

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of thiophen-2-yl, phenyl, 2,5-dichlorophenyl, 2-nitrophenyl, 4-bromophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-(trifluoromethyl)phenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 2,3-dichlorophenyl, 2-bromophenyl, 5-(2-pyridyl)thiophen-2-yl, 2-chloro-5-(trifluoromethyl)phenyl, 4-cyanophenyl, 2-

cyanophenyl, 5-chloro-1,3-dimethylpyrazol-4-yl, 3,5-dimethylisoxazol-4-yl, 2,4-dichlorophenyl, 2-chloro-4-(trifluoromethy)lphenyl, 2-chloro-4-fluorophenyl, 2,4,6-trichlorophenyl, 1-methylimidazol-4-yl, 2-methoxycarbonythiophen-3-yl, 5-(isoxazol-3-yl)thiophen-2-yl, 4-phenylphenyl, 3,4-difluorophenyl, 3-methyl-5-chlorobenzothiophen-2-yl, 3-cyanophenyl, 4-methylsulfonylphenyl and 2-methylsulfonylphenyl;

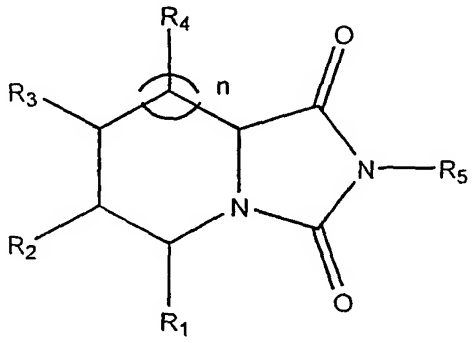
R_7 is the formula -D-W-, wherein:
W is absent and D is selected from the group consisting of phenylethyl-1-ene, ethyl-1-ene, propyl-1-ene, propylene, pentylene, 4-(chlorophenyl)ethyl-1-ene, 3-(methylthio)propyl-1-ene, 4-(methoxyphenyl)ethyl-1-ene, 2-methylpropyl-1-ene, 2-(4-imidazole)ethyl-1-ene, 2-(benzyloxy)ethyl-1-ene, 3-methylbutyl-1-ene and 2-cyclohexylethyl-1-ene; or D is methylene and W is selected from the group consisting of 4-phenylene and 4-cyclohexylene; and

R_8 is $-C(O)NR_9R_{10}$, wherein one of R_9 and R_{10} is selected from the group consisting of a functionalized resin and a hydrogen atom, and the other is a hydrogen atom; and

R_5 is selected from the group consisting of phenyl, 2-bromophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2-methoxyphenyl, O-tolyl, 2-ethylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, m-tolyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, p-tolyl,

1-naphthyl, benzyl, 2-isopropylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2-ethyl-6-methylphenyl, 3-(methylthio)phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2-methoxy-5-methylphenyl, 3-ethylphenyl, 4-ethoxyphenyl, 4-(methylthio)phenyl, 4-isopropylphenyl, 4-ethylphenyl, 4-n-butylphenyl, 2-isopropyl-6-methylphenyl, 2,4,5-trimethylphenyl, 4-butoxyphenyl, 5-fluoro-2-methylphenyl and 4-(dimethylamino)phenyl.

8. A single compound of the formula:



wherein:

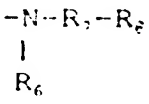
n is 0, 1 or 2;

a) R_1; b) when n is 0, R_3; c) when n is 1, R_4 and one of R_2 and R_3; and d) when n is 2 an addition radical between R_3 and R_4, R_{34}, is present and, when n is 2, R_4 and two of R_2, R_3 and R_{34}:

are each independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl,

C_7 to C_{18} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, carboxy and protected carboxy; and

a) when n is 0, R_2; b) when n is 1, one of R_2 and R_3; and c) when n is 2 one of R_2, R_3 and R_{34}:
is selected from the group consisting of amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino and the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is selected from the group consisting of -C(O)-, -C(O)O- and $-S(O)_2-$ and M is selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_7 is the formula -D-W-E-, wherein at least one of D, W and E is present and the other two are optionally present or absent, and wherein:
W is selected from the group consisting of C_3 to C_7

cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene; and D, which, if present, is directly attached to the nitrogen depicted in the formula, and E are independently selected from the group consisting of C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene and C_2 to C_{12} substituted alkynylene;

R_8 is selected from the group consisting of a hydrogen atom, a halide, $-OR_9$, $-CO_2R_9$, $-C(O)NR_9R_{10}$ and $-NR_9R_{10}$, wherein R_9 and R_{10} are independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl; and

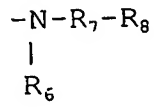
R_5 is selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, heterocyclic ring and substituted heterocyclic ring, or the group consisting of (i) the formula $-C(O)R_{11}$; (ii) the formula $-C(O)OR_{11}$; (iii) the formula $-C(O)NHR_{11}$; (iv) the formula $-C(O)NR_{11}R_{12}$; and (v) the formula $-S(O_2)R_{11}$, wherein R_{11} and R_{12} are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl,C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} substituted heterocycloalkyl, heterocyclic ring and substituted heterocyclic ring, or R_5, together with the adjoining nitrogen atom depicted in the formula, form a heterocyclic ring or substituted heterocyclic ring, wherein said ring is non-aromatic.

9. The single compound of claim 8, wherein n is 0.

10. The single compound of claim 9, wherein R_1 and R_3 are each a hydrogen atom.

11. The single compound of claim 9, wherein

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of a phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl and substituted heteroaryl;

R_7 is the formula -D-W-, wherein D is present and W is optionally present or absent, and wherein: D is selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and W is selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, arylene and substituted arylene; and

R_8 is $-C(O)NH_2$.

12. The single compound of claim 8, wherein

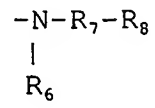
R_5 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl and C_7 to C_{18} substituted phenylalkyl.

13. The single compound of claim 8, wherein:

n is 0;

R_1 and R_3 are each a hydrogen atom;

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl and substituted heteroaryl;

R_7 is the formula -D-W-, wherein D is present and W is optionally absent or present, and wherein: D is selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and W is selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, arylene and substituted arylene; and

R_8 is $-C(O)NH_2$; and

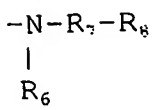
R_5 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl and C_7 to C_{18} substituted phenylalkyl.

14. The single compound of claim 8, wherein:

n is 0;

R_1 and R_3 are each a hydrogen atom;

R_2 is the formula:



wherein:

R_6 is the formula -L-M, wherein -L- is $-S(O)_2-$ and M is selected from the group consisting of thiophen-2-yl, phenyl, 2,5-dichlorophenyl, 2-nitrophenyl, 4-bromophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-(trifluoromethyl)phenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 2,3-dichlorophenyl, 2-bromophenyl, 5-(2-pyridyl)thiophen-2-yl, 2-chloro-5-(trifluoromethyl)phenyl, 4-cyanophenyl, 2-cyanophenyl, 5-chloro-1,3-dimethylpyrazol-4-yl, 3,5-dimethylisoxazol-4-yl, 2,4-dichlorophenyl, 2-chloro-4-(trifluoromethy)lphenyl, 2-chloro-4-fluorophenyl, 2,4,6-trichlorophenyl, 1-methylimidazol-4-yl, 2-methoxycarbonythiophen-3-yl, 5-(isoxazol-3-yl)thiophen-2-yl, 4-phenylphenyl, 3,4-difluorophenyl, 3-methyl-5-chlorobenzothiophen-2-yl, 3-cyanophenyl, 4-methylsulfonylphenyl and 2-methylsulfonylphenyl;

R_7 is the formula -D-W-, wherein:
W is absent and D is selected from the group consisting of phenylethyl-1-ene, ethyl-1-ene, propyl-1-ene, propylene, pentylene, 4-(chlorophenyl)ethyl-1-ene, 3-(methylthio)propyl-1-ene, 4-(methoxyphenyl)ethyl-1-ene, 2-methylpropyl-1-

ene, 2-(4-imidazole)ethyl-1-ene, 2-(benzyloxy)ethyl-1-ene, 3-methylbutyl-1-ene and 2-cyclohexylethyl-1-ene; or D is methylene and W is selected from the group consisting of 4-phenylene and 4-cyclohexylene; and

R_3 is $-C(O)NH_2$; and

R_5 is selected from the group consisting of phenyl, 2-bromophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2-methoxyphenyl, O-tolyl, 2-ethylphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, m-tolyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, p-tolyl, 1-naphthyl, benzyl, 2-isopropylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2-ethyl-6-methylphenyl, 3-(methylthio)phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2-methoxy-5-methylphenyl, 3-ethylphenyl, 4-ethoxyphenyl, 4-(methylthio)phenyl, 4-isopropylphenyl, 4-ethylphenyl, 4-n-butylphenyl, 2-isopropyl-6-methylphenyl, 2,4,5-trimethylphenyl, 4-butoxyphenyl, 5-fluoro-2-methylphenyl and 4-(dimethylamino)phenyl.

15. A method of preparing a bicyclic hydantoin derivative, comprising:

(a) coupling (i) a molecule containing a group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$, wherein R_1 and R_2, independently, are each a variable group, with (ii) a ring nitrogen compound, wherein said ring is non-aromatic, wherein said compound is substituted at the position adjacent to the ring nitrogen with -C(O)-O-alkyl, and further substituted with a hydroxy group, resulting a ring nitrogen compound that is

substituted at the position adjacent to the ring nitrogen with -C(O)-O-alkyl and further substituted with a group of the formula $-N(S(O_2)-R_2)-R_1-C(O)-NH-$;

(b) reacting the resulting compound of step (a) with an isocyanate of the formula R_3-NCO, where R_3 is a variable group, to form a $-C(O)-NH-R_3$ group attached to the ring nitrogen; and

(c) cyclizing the resulting compound of step (b) by reacting it with a base to form a bicyclic hydantoin derivative.

16. The method of claim 15, wherein said alkyl is selected from the group consisting of methyl and ethyl.

17. The method of claim 15, wherein said base is selected from the group consisting of tetramethylguanidine and barium hydroxide.

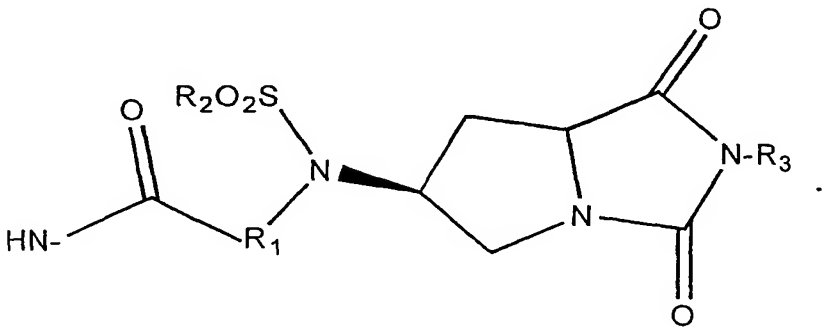
18. The method of claim 15, wherein the molecule containing the group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ is attached to a functionalized resin.

19. The method of claim 15, wherein the molecule containing the group of the formula $-NH-C(O)-R_1-NH-S(O_2)-R_2$ is formed by coupling a molecule containing a group of the formula $-NH-C(O)-R_1-NH_2$ with a molecule of the formula $R_2-S(O_2)-$leaving group.

20. The method of claim 19, wherein the leaving group is a halide.

21. The method of claim 20, wherein the halide is chloride.

22. The method of claim 15, wherein the ring nitrogen compound is a pyrrolidine derivative and the hydroxy group is at the 4-position of the pyrrolidine, resulting in a compound after performing step (c) of the formula:



23. The method of claim 15, wherein the ring nitrogen compound is a six or seven member ring.

24. The method of claim 23, wherein the ring nitrogen compound is a piperidine derivative.

25. The method of claim 23, wherein the ring contains a double bond.

26. The method of claim 15, wherein the ring nitrogen compound is fused to another ring.

27. A method of preparing a bicyclic hydantoin derivative, comprising:

(a) coupling (i) a ring nitrogen compound, wherein said ring is non-aromatic, wherein said ring is attached to a group containing -C(O)-O-, said ring directly attached from a position adjacent to the ring nitrogen to the carbonyl carbon of said -C(O)-O-, with (ii) an isocyanate derivative of the formula variable-NCO to form (iii) a ring nitrogen compound with the group -C(O)-NH-variable directly attached to the ring nitrogen; and

(b) cyclizing the resulting compound of step (a) by reacting it with a base to form a bicyclic hydantoin derivative.

28. The method of claim 27, wherein said base is selected from the group consisting of tetramethylguanidine and barium hydroxide.

29. The method of claim 27, wherein the group containing -C(O)-O- is attached to a functionalized resin via oxygen.

30. The method of claim 27, wherein the ring nitrogen is five-member.

31. The method of claim 27, wherein the ring nitrogen is six-member.

Scheme 1

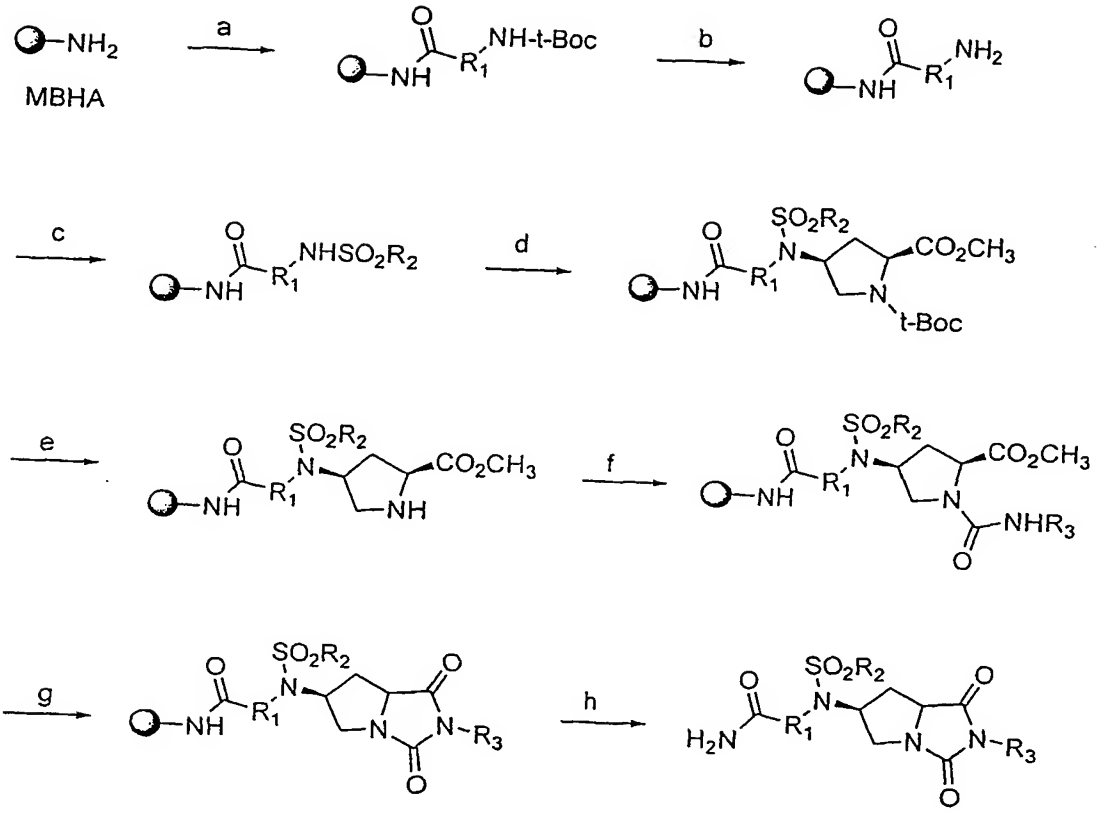


FIGURE 1

Scheme 2

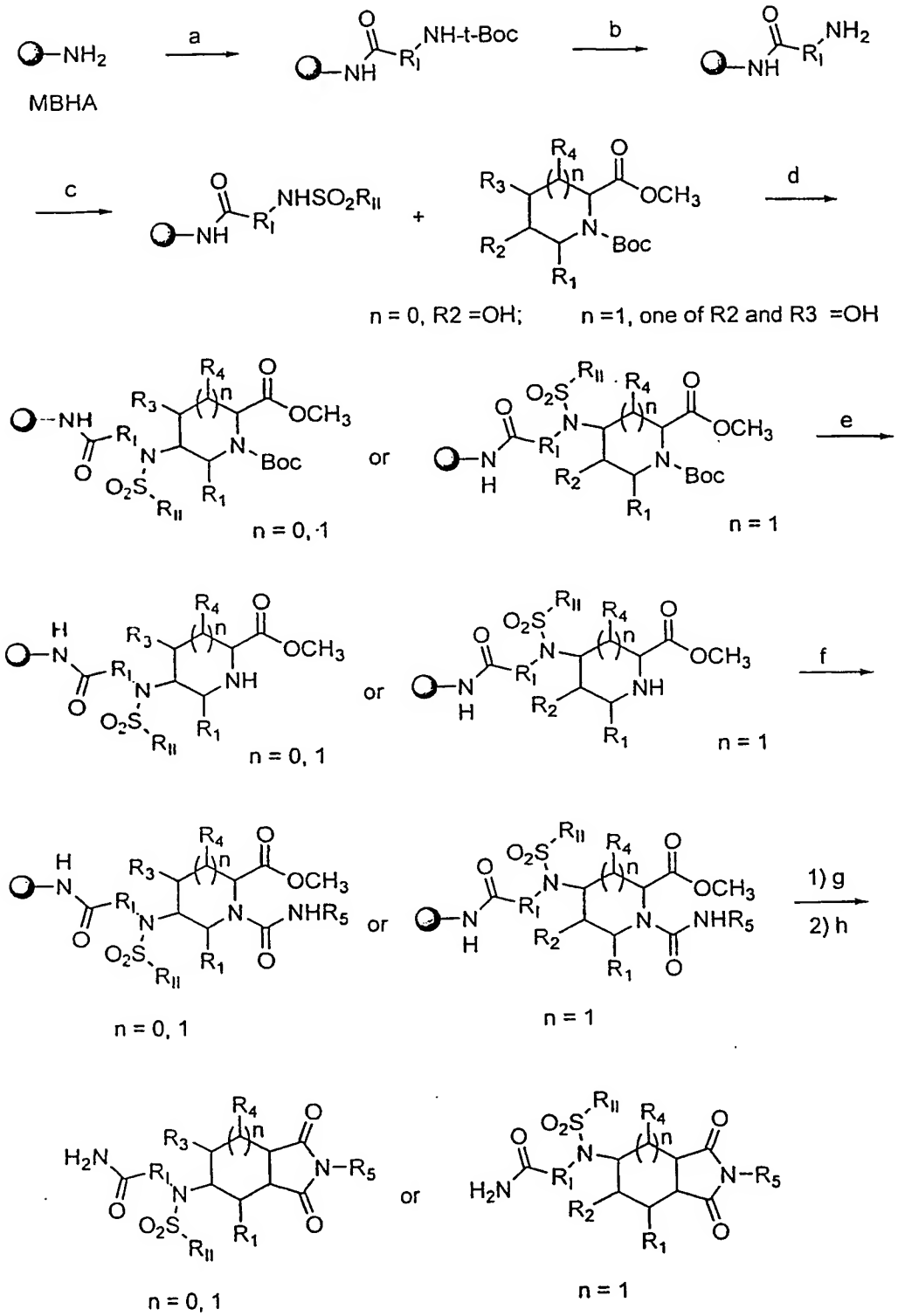
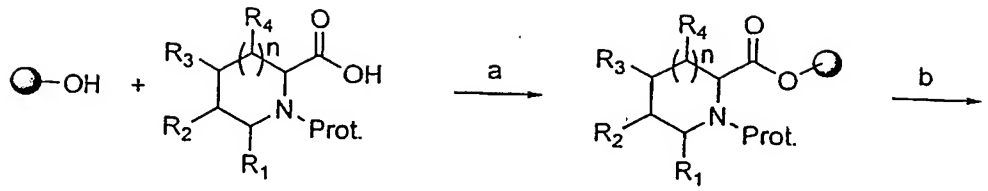


FIGURE 2

Scheme 3



n = 0, 1, 3; Prot. = Fmoc., Boc., ect.

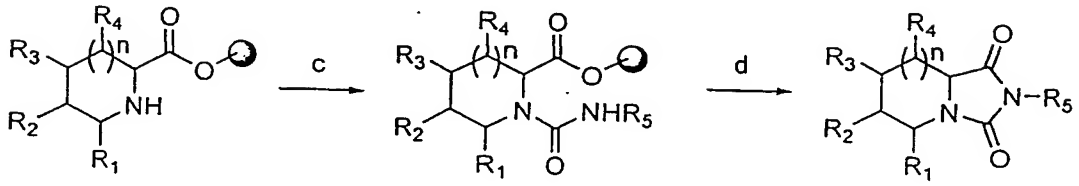


FIGURE 3